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A STUDY OF RENAL FUNCTION AND THE ASSOCIATED DISTURBANCE IN THE ACID-BASE EQUILIBRIUM OF THE BLOOD IN CERTAIN EXPERIMENTAL AND NATURALLY ACQUIRED NEPHROPATHIES *

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During the past fourteen years, the work in this laboratory has been confined largely to a study of different types of acute experimental nephropathy and of certain naturally acquired chronic nephropathies. Four hundred and forty-nine animals have been employed in the various series of experiments. In a large number of these animals some form of renal functional test was used. In 132 animals a functional study of the kidney was the primary object of the investigation. In this latter group of animals a variety of functional tests were made use of. With this large amount of experimental data available, a study has been undertaken of the function of the kidney in different types of nephropathic processes and of the association of changes in the acid-base equilibrium of the blood with variations in the functional and pathological response on the part of the kidney.

In the earlier series of experiments [1] which had as their object a study of the pathology of the acutely nephropathic kidney various substances were employed in an attempt to obtain some nephrotoxic agent which would produce in the kidney of the dog a reaction comparable to the acute nephropathy found in human material, in which the renal epithelium is primarily and more severely involved than is the vascular or interstitial tissue. The nephrotoxic agent which more nearly produces this type of reaction on the part of the kidney is uranium in the form of the nitrate. Christian and O'Hare [2] have shown that in the rabbit, uranium induces an early injury to the glomerular vessels. In

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1. MacNider, William deB.: A Study of the Renal Epithelium in Various Types of Acute Experimental Nephritis and of the Relation which Exists Between the Epithelial Changes and the Total Output of Urine, J. Med. Res. 21:79, 1912.

2. Christian, Henry A., and O'Hare, James P.: Glomerular Lesions in Acute Experimental (Uranium) Nephritis in Rabbits, J. Med. Res. 28:227, 1913.

a later communication O'Hare [3] has pointed out the difficulty of inducing these changes in the glomerular vessels of the dog's kidney. From a large number of experiments on dogs I can confirm this observation. When uranium is given subcutaneously to the dog in small doses, properly spaced, the injury induced in the kidney is characterized by an acute tubular injury with an acute engorgement of the renal vessels, occasionally a small amount of exudate into the subcapsular space, but without degeneration in the vascular tissue. Substances such as the tartrates that have recently been employed by Underhill, Wells and Goldschmidt [4] as nephrotoxic agents are too selective in their affinity for the tubular epithelium and produce too rapidly an extensive necrosis of this tissue for them to be employed in experiments in which an attempt is made to duplicate experimentally the acute pathology found in certain of the acute nephropathies of human material. A second consideration which makes uranium an especially appropriate substance to use in such experimental studies, is that during the recovery of the kidney from the acute injury the processes of repair as was shown by Dickson [5] for the kidney of the guinea-pig, and more recently by MacNider [6] for the kidney of the dog, lead to the development of a chronic diffuse type of nephropathy. In this chronic nephropathy the glomeruli show both a capsular and intracapillary type of injury. The tubules show changes of repair in the regeneration of a flattened type of epithelium, which takes the place of the more specialized cells. Furthermore, functional studies in such nephropathic animals show these kidneys to resemble very closely the chronic diffuse nephropathy of human material, which originates as a reaction of repair to some diffusely acting nephrotoxic agent.

In the studies from this laboratory [7] on the chronic naturally acquired nephropathy of the dog, it was shown that the more common

3. O'Hare, James P.: Acute Renal Lesions Produced by Uranium Nitrate in the Dog in Comparison with the Rabbit, Arch. Int. Med. **12**:61, 1913.

4. Underhill, Frank P., Wells, H. Gideon and Goldschmidt, Samuel: Tartrate Nephritis, with Special Reference to Some of the Conditions Under which It May Be Produced, J. Exper. Med. **18**:322, 1913.

5. Dickson, Ernest C.: A Report on the Experimental Production of Chronic Nephritis in Animals by the Use of Uranium Nitrate, Arch. Int. Med. **3**:375, 1909.

A Further Report on the Production of Experimental Chronic Nephritis in Animals by the Administration of Uranium Nitrate, Arch. Int. Med. **9**:557, 1912.

6. MacNider, William deB.: A Functional and Pathological Study of the Chronic Nephropathy Induced in the Dog by Uranium Nitrate, J. Exper. M. **29**:513, 1919.

7. MacNider, William deB.: A Pathological Study of the Naturally Acquired Chronic Nephropathy of the Dog, Part I, J. Med. Res. **34**:177, 1916.

A Pathological and Physiological Study of the Naturally Nephropathic Kidney of the Dog Rendered Acutely Nephropathic by Uranium or by an Anesthetic, J. Med. Res. **34**:199, 1916.

type of injury was one in which the glomerulus was damaged out of proportion to the degree of tubular injury. This observation has been recently confirmed for human material by Stengel, Austin and Jonas.[8] Functional studies have been made in these naturally nephropathic animals and at a later period an acute tubular injury has been superimposed on the chronic pathology by employing uranium nitrate or mercuric chlorid. In these animals functional tests have again been employed to study the effect on function of the acute injury. By such a procedure it has been found possible to induce in the dog a pathologic condition and a functional response very similar to that obtained in human material in which an acute condition develops during the course of a chronic nephropathy and which not infrequently serves as a terminal change.

In the following study of renal functional tests, the observations will be confined to the functional response of the kidney in three types of injury. First, the function of the kidney will be studied in the earlier stages of an acute uranium intoxication when the pathology of the kidney is very largely confined to the tubular epithelium. In the second group of animals, observations will be made on the functional response of the kidney late in the uranium intoxication, when as a result of the processes of repair in both the tubules and the glomeruli a subacute or chronic nephropathy is being produced. The third group of animals is represented by dogs with a chronic naturally acquired nephropathy in which the renal injury is very largely confined to the glomeruli. At a later period in the study of these naturally nephropathic animals, renal functional tests have been employed after an acute process of epithelial degeneration had been superimposed on the chronic pathology by the use of uranium nitrate or mercuric chlorid.

TECHNIC OF EXPERIMENTS

All of the animals employed in this study, whether normal or naturally nephropathic, have been subjected to a routine type of study both before and during the course of the experiments. One hundred and five animals have been employed in the various groups of experiments. In Group I, thirty-two animals have been studied during the early stages of an acute uranium intoxication. Twenty-eight animals have been employed in Group II, representing the later stages in an acute uranium intoxication, in which the changes of repair lead to the development of a chronic nephropathy. Forty-five animals have been used in Group III. This group is composed of naturally nephropathic

8. Stengel, A., Austin, J. H., and Jonas, L.: A Comparison of the Functional Findings in a Series of Cases of Renal Disease, Arch. Int. Med. **21:** 313, 1918.

animals. In these animals an acute epithelial injury has been super-
imposed on the chronic naturally acquired pathology. All of the ani-
males were kept in metabolism cages for from two to four days before
any experimental procedure was commenced. During this period and
after the commencement of the experiments, the animals were fed on
bread containing a small amount of cooked meat. The animals received
by stomach tube, once a day, 500 c.c. of water. Those animals which
were used during the summer months were watered twice a day. The
female dogs were catheterized either once or twice a day, and the urine
mixed with the cage urine for analysis. All of the animals, except a
certain number of the naturally nephropathic animals, which were given
mercuric chlorid, at some stage of the experiment received subcutane-
ously 4 mg. per kilogram of uranium nitrate at one injection. Both
before and after the commencement of the experiments the following
observations have been made. The urine was subjected to the ordi-
nary qualitative analysis. Quantitative determinations of albumin were
made with both Esbach's and Tsuchiya's reagents. The output of
acetone and diacetic acid was determined by the method of Folin [9] as
modified by Hart.[10] The phenolsulphonephthalein elimination was
determined for two hour periods according to the technic devised by
Rowntree and Geraghty.[11] The centrifugalized urines were examined
for casts. Blood urea determinations were made by the method of
Marshal [12] as modified by Van Slyke and Cullen.[13] The estimations of
blood creatinin were made by colorimetric determinations. A standard
solution of creatinin in saturated picric acid was employed in prefer-
ence to the standard potassium dichromate solution. The former solu-
tion is more accurate. In studying the changes in the acid-base equilib-
rium of the blood, the methods of Marriott [14] have been employed to
ascertain the alkali reserve of the blood and the tension of alveolar air
carbon dioxid.

9. Folin, O.: On the Separate Determinations of Acetone and Diacetic
Acid in Diabetic Urines, J. Biol. Chem. **3**:177, 1907.

10. Hart, T. S.: On the Quantitative Determination of Acetone in the
Urine, J. Biol. Chem. **4**:477, 1908.

11. Rowntree, L. G., and Geraghty, J. T.: An Experimental and Clinical
Study of the Functional Activity of the Kidneys by Means of Phenolsulphone-
phthalein, J. Pharmacol. & Exper. Therap. **1**:579, 1909.

12. Marshall, E. K., Jr.: A Rapid Clinical Method for the Estimation of
Urea in Urine, J. Biol. Chem. **14**:283, 1913.

13. Van Slyke, D. D., and Cullen, G. E.: A Permanent Preparation of
Urease, and Its Use in the Determination of Urea, J. Biol. Chem. **19**:211, 1914.

14. Marriott, W. McK.: A Method for the Determination of the Alkali
Reserve of the Blood Plasma, Arch. Int. Med. **17**:840, 1916.

Marriott, W. McK.: The Determination of Alveolar Carbon Dioxid Tension
by a Simple Method, J. A. M. A. **66**:1594 (May 20) 1916.

GROUP I. A FUNCTIONAL AND PATHOLOGIC STUDY OF THE KIDNEY IN
THE EARLY STAGES OF AN ACUTE URANIUM
NEPHROPATHY

In previous publications [15] the observation has been recorded that
the toxicity of uranium for the dog is very definitely associated with
the age of the animal. Regardless of the weight of the animal,
uranium is more toxic for the older animals than for the young animals.
This is shown in the rapidity of the development and the severity of
the kidney injury. This factor, together with the dose of uranium and
the duration of the intoxication, has to be taken into consideration in
order to obtain a nephropathy typical for the early stages of a uranium
intoxication. In this first group of acutely nephropathic animals, this
factor of the age of dogs has been taken into consideration. The
experiments as detailed in Tables 1, 2, 3 and 4, not only show the

TABLE 1.—GROUP I, EXPERIMENT 4. ACUTE URANIUM NEPHROPATHY

Animal: Age, 7 years; weight, 15.2 kg.

Day of Exp.	Water in 24 Hrs., C.c.	Uranium Nitrate per Kg.	Urine in 24 Hrs., C.c.	Albumin and Casts	Acetone, Mg. per 100 C.c.	Diacetic Acid, Mg. per 100 C.c.	Blood Urea, Mg. per 100 C.c	Blood Creatinin, Mg. per 100 C.c.	Phthalein 2 Hrs., per Cent.	R. p. H.	Carbon Dioxid Tension, Mm.
Normal	500	0	399	0	0	0	18	1.98	84	8.1	45
1	500	4 mg.	915	2 gm. Numerous casts	0	0	59	2.41	20	7.9	33
2	500	....	697	3.6 gm. Numerous casts	1.632	3.265	72	3.81	Trace	7.85	27
4	500	....	71	2 gm.	2.425	2.099	117	5.72	0	7.75	19
6	500	....	74	Trace	0	1.162	284	7.64	0	7.7	12

course of the intoxication in its early stages, but also serve to empha-
size the importance of the age of the animal in determining the
acuteness and severity of the intoxication. Thirty-two dogs were
employed in this first group of experiments. The animals were kept
in metabolism cages and normal observations made for two to four
days. A one-day period of normal observations is included at the
commencement of each table. After the period of normal observation
the animals received one subcutaneous injection of 4 mg. per kilogram
of uranium nitrate. All of the experiments were terminated on the
sixth day of the intoxication. An anesthetic was not employed for this
purpose. As has been previously shown,[16] the acutely nephropathic

15. MacNider, William deB.: A Consideration of the Relative Toxicity of
Uranium Nitrate for Animals of Different Ages, J. Exper. Med. **26**:1, 1917.
    MacNider, William deB.: Concerning the Influence of the Age of an Organ-
ism in Maintaining Its Acid-Base Equilibrium, Science **46**:643, 1917.
    16. MacNider, William deB.: The Effect of Different Anesthetics on the
Pathology of the Kidney in Acute Uranium Nephritis, J. Med. Res. **27**:403, 1913.

kidney is extremely sensitive to the effect of the general anesthetics. If an anesthetic is employed in such an experiment the epithelial pathology of the kidney is grossly altered from the reaction induced by the nephrotoxic agent.

TABLE 2.—GROUP I, EXPERIMENT 18. ACUTE URANIUM NEPHROPATHY
Animal: Age, 13 months; weight, 12.58 kg.

Day of Exp.	Water in 24 Hrs., C.c.	Uranium Nitrate per Kg.	Urine in 24 Hrs., C.c.	Albumin and Casts	Acetone, Mg. per 100 C.c.	Diacetic Acid, Mg. per 100 C.c.	Blood Urea, Mg. per 100 C.c.	Blood Creatinin, Mg. per 100 C.c.	Phthalein 2 Hrs., per Cent.	R. p. H.	Carbon Dioxid Tension, Mm.
Normal	500	0	302	0	0	0	18	2.51	81	8.0	40
1	500	4 mg.	619	0.75 gm. No casts	8.863	2.799	28	2.58	56	7.95	38
2	500	0	300	2.7 gm. Casts present	3.825	1.816	59	3.41	0	7.9	34
4	500	0	412	0.5 gm.	3.614	1.532	81	5.71	0	7.85	53
6	500	0	281	Trace	3.021	1.502	146	5.79	0	7.85	30

TABLE 3.—GROUP I, EXPERIMENT 6. ACUTE URANIUM NEPHROPATHY
Animal: Age, 1 year; weight, 12.33 kg.

Day of Exp.	Water in 24 Hrs., C.c.	Uranium Nitrate per Kg.	Urine in 24 Hrs., C.c.	Albumin and Casts	Acetone, Mg. per 100 C.c.	Diacetic Acid, Mg. per 100 C.c.	Blood Urea, Mg. per 100 C.c.	Blood Creatinin, Mg. per 100 C.c.	Phthalein 2 Hrs., per Cent.	R. p. H.	Carbon Dioxid Tension, Mm.
Normal	500	0	500	0	0	0	17	1.85	83	8.05	41
1	500	4 mg.	485	0.4 gm. No casts	8.863	9.796	16	1.77	75	7.95	38
2	500	0	369	1.0 gm. Few casts	5.364	14.228	16	1.87	67	7.95	38
4	500	0	530	1.75 gm. Numerous casts	14.928	17.727	45	2.31	Trace	7.85	26
6	500	0	320	0.9 gm. Numerous casts	5.598	7.230	59	4.81	0	7.75	18

TABLE 4.—GROUP I, EXPERIMENT 20. ACUTE URANIUM NEPHROPATHY
Animal: Age, 11 months; weight, 6.8 kg.

Day of Exp.	Water in 24 Hrs., C.c.	Uranium Nitrate per Kg.	Urine in 24 Hrs., C.c.	Albumin and Casts	Acetone, Mg. per 100 C.c.	Diacetic Acid, Mg. per 100 C.c.	Blood Urea, Mg. per 100 C.c.	Blood Creatinin, Mg. per 100 C.c.	Phthalein 2 Hrs., per Cent.	R. p. H.	Carbon Dioxid Tension, Mm.
Normal	500	0	412	0	0	0	15	2.0	78	8.0	40
1	500	4 mg.	261	Trace No casts	8.630	3.032	15	2.0	60	7.95	37
2	500	0	375	0.6 gm. Few casts	28.923	39.186	22	2.31	51	7.9	33
4	500	0	339	1.4 gm. Few casts	4.009	8.086	48	3.82	30	7.9	33
6	500	0	230	Trace	5.134	4.721	80	4.71	0	7.75	20

A study of Tables 1, 2, 3 and 4 shows all of the animals to be normal prior to the use of uranium. The daily output of urine has varied from a minimum of 71 c.c. to a maximum of 915 c.c. The urine of all

of the animals was free from albumin and casts, and acetone and diacetic acid. The normal blood urea determinations varied from 15 to 18 mg. per hundred c.c. of blood. The blood creatinin determinations varied from 1.85 to 2.51 mg. per hundred c.c. of blood. The estimations have been very constant. In our experience, the blood creatinin for dogs has been somewhat higher than the findings of Myers and Lough [17] for human blood. The elimination of phenolsulphonephthalein in a two-hour period has varied between 69 and 84 per cent. The reserve alkali of the blood for the normal animals has varied between 8.0 to 8.1. The tension of alveolar air carbon dioxid in the different animals has shown a close correlation with the determinations of the alkali reserve. The tension of carbon dioxid in alveolar air has varied between 40 to 45 mm. of mercury. In two of the older animals of this series there was a lack of correlation between the determinations of the alkali reserve of the blood and the tension of carbon dioxid in alveolar air. At necropsy both of these dogs showed an advanced stage of pulmonary emphysema.

Following the commencement of the uranium intoxication, the effect on the daily output of urine is variable. In some of the animals there occurs an initial polyuria. This was the case in the animal of Experiment 4, Table 1. The output of urine increased from 390 c.c. on the day prior to the uranium to 915 c.c. on the first day of the uranium intoxication. In other animals, as is shown in the tables, the daily output of urine remains unchanged, or a slight reduction occurs. In all of the animals of this group albumin appeared in the urine within the first twenty-four hours. At this very early stage of the kidney injury, the association of casts with the albumin was variable. In those animals in which only a trace of albumin was found in the urine casts have frequently not been present. In those animals in which 1 gm. or more of albumin appeared in the urine casts have invariably been present. In animals which have been killed at this very early stage of the nephropathy in which the urine showed a trace of albumin but no casts, the pathology of the kidney has consisted in an acute engorgement of the glomerular tufts and no epithelial degeneration. In those animals that have shown both an albuminuria and casts, the renal epithelium has shown an early degeneration. From this observation it would appear that cast formation is more definitely associated with epithelial injury than it is with the contact of blood albumin with the acid environment of the kidney. A study of the four tables of experiments representing this group of animals shows the old animals of the group to have a higher percentage of albumin in the urine on the

17. Myers, Victor C., and Lough, Walter G.: Creatinin of the Blood in Nephritis. Its Diagnostic Value, Arch. Int. Med. **16**:536, 1915.

first and subsequent days of the experiments than do the young animals. This has been a very constant observation, and was the first point to call attention to the difference in the response of animals of different ages to a constant quantity of uranium. As will be noted, with the appearance of albumin in the urine there also occurs a reduction in the reserve alkali of the blood, a decrease in the tension of alveolar air carbon dioxid, and a sharp reduction in the elimination of phenolsulphonephthalein. In our long series of experiments there has been a constant association between the depletion of the blood of its alkali reserve from the use of uranium and the appearance of albumin in the urine. It is difficult to say that the reduction in the reserve alkali of the blood is the cause of the albuminuria. It can, however, be stated that with the reduction in the alkali reserve of the blood which is effected by uranium there is an associated albuminuria. In a recent research by Karsner[18] on the toxic effect of uranium in dogs he has confirmed the occurrence of a depletion of the alkali reserve of the blood with the beginning of the kidney injury. In a certain number of his animals the albuminuria developed prior to the reduction of the alkali reserve of the blood. This has not occurred in our studies with a large number of animals. We have found a constant association between the reduction in the reserve alkali of the blood and the appearance of albumin in a specimen of catheterized urine obtained at the same time that the alkali reserve determination was made.

A further study of the tables of experiments of this group of acutely nephropathic animals shows that not only is the output of albumin in the urine greater in the older animals, but the reduction in the elimination of phenolsulphonephthalein, the depletion of the reserve alkali of the blood, and the decrease in the tension of alveolar air carbon dioxid, are all more sharply affected than is the case with the younger animals of the group. The animal of Experiment 4, Table 1, 7 years old, on the first day of the uranium intoxication showed an albuminuria of 2 gm. per liter, a reduction in the output of phenolsulphonephthalein from a normal of 84 per cent. to 20 per cent., a depletion in the reserve alkali of the blood from a normal of 8.1 to 7.9 and a reduction of the carbon dioxid tension of alveolar air from 45 to 33 mm. The young animal of Group 1, Table 4, Experiment 20, 11 months old, showed during the first day of the uranium intoxication only a trace of albumin in the urine. The phenolsulphonephthalein elimination was only reduced from a normal of 78 per cent. to 60 per

18. Karsner, Howard T., Reimann, Stanley P., and Brooks, S. C.: Studies of Uranium Poisoning. IV. The Relation of Acid Intoxication to Nephritis, J. Med. Res. **39**:177, 1918.

cent., the reserve alkali of the blood was reduced from 8.0 to 7.95, and the tension of carbon dioxid in alveolar air was reduced from 40 to 33 mm.

A further study of the albuminuria during these experiments shows that as the severity of the kidney injury progresses, as indicated by a continuous reduction in the output of phenolsulphonephthalein, there occurs a decrease in the amount of albumin in the urine. Associated with the diminishing ability of the kidney to secrete phenolsulphone-phthalein, there occurs a progressive reduction in the alkali reserve of the blood. There is a definite association between the severity of the kidney injury as shown by the phenolsulphonephthalein elimination and the depletion of the blood of its alkali reserve. There is, however, no correlation between the elimination of this dye and the disturbance in the acid-base equilibrium of the blood with the quantitative output of albumin in the urine. As will be seen in Experiment 4, on the second day of the uranium intoxication the urine showed 3.6 gm. of albumin per liter, the phenolsulphonephthalein elimination for two hours was only a trace and the alkali reserve of the blood showed a depletion to 7.85. On the sixth day of the experiment, with the total output of urine reduced to 74 c.c., the urine contained only a trace of albumin. The phenolsulphonephthalein output was negative, the reserve alkali of the blood was reduced to 7.7 and the tension of carbon dioxid in alveolar air was reduced to 12 mm. These experiments indicate very clearly that determinations of the quantitative output of albumin in the urine may give an entirely erroneous conception of the severity of the kidney injury. Each day during the course of these experiments at the same time that the previously mentioned observations were made, examinations of the blood were undertaken for evidence of kidney injury as indicated by a retention of blood urea and creatinin.

A study of the four tables of experiments in this group of animals shows that a retention of both urea and creatinin occurs not later than the second day of the acute kidney injury. Table 1, Experiment 4, which represents the older animals of the group, shows a retention of urea and creatinin on the first day of the experiment, while in the younger animals as indicated by Table 4, Experiment 20, there is no retention of these substances as early as the first day of the experiment, and not until the fourth day is the retention marked.

The various tables of experiments also show a definite correlation between the severity of the kidney injury as indicated by the elimination of phenolsulphonephthalein and the degree of depletion of the blood of its alkaline reserve with a retention of both urea and creatinin. In the old animal of Experiment 4, during the first day of the kidney

injury from uranium, the elimination of phenolsulphonephthalein was reduced from a normal of 84 per cent. to 20 per cent., and the alkali reserve of the blood was depleted from 8.1 to 7.9. During this period a retention of blood urea occurred from a normal of 18 mg. per hundred c.c. to 59 mg. The blood creatinin showed a retention from a normal of 1.98 mg. to 2.41 mg. In the case of the younger animal of Table 4, Experiment 20, with a less severe kidney injury, the same evidence of diminished renal function was shown, but the reduction in renal function developed more gradually. In this animal, on the first day of the renal injury, the phenolsulphonephthalein elimination was only reduced from a normal of 78 per cent. to 60 per cent., and the reserve alkali was only reduced from 8.0 to 7.95. During this first day there was no retention of either blood urea or creatinin. As the kidney injury progressed, as was shown by a further reduction in the elimination of phenolsulphonephthalein, there occurred both a retention of blood urea and creatinin. On the fourth day of this experiment, the elimination of phenolsulphonephthalein was 30 per cent., the blood urea retention was 80 mg. per hundred c.c., and the creatinin retention 4.91 mg.

From these observations it is clear that the earliest evidence of renal injury consists in a reduction in the output of phenolsulphonephthalein and the appearance of albumin in the urine. After a certain grade of renal injury is established there then occurs a retention of both urea and creatinin. During the remaining days of the experiments there has occurred with a progressive decrease in the ability of the kidney to eliminate phenolsulphonephthalein an increase in the retention of blood urea and creatinin. In the animal of Experiment 1, with a very severe kidney injury there was a retention of blood urea on the sixth day of the experiment of 284 mg., and a creatinin retention of 7.64 mg. In the animal of Experiment 20, with a less severe kidney injury, the blood urea retention was 80 mg., and the creatinin retention 4.71 mg.

During the course of these experiments determinations have been made of the time of appearance and quantitative output in the urine of both acetone and diacetic acid. These observations have been made in connection with changes in the alkali reserve of the blood and with the disturbance in renal function. A study of the table of experiments shows that the appearance of acetone and diacetic acid in the urine may or may not occur with the initial reduction in the alkali reserve of the blood. In Experiment 4, Table 1, the alkali reserve of the blood was reduced during the first day of the experiment from 8.1 to 7.9. The urine was free from both acetone and diacetic acid. In other animals of this group, Tables 2, 3 and 4, with a reduction in the alkali reserve, there also appeared in the urine both acetone and diacetic acid.

During the remaining days of the experiments with a progressive depletion in the alkali reserve, the output of acetone and diacetic acid in the urine not only failed to show an increase, but the output of both of these bodies was finally diminished.

A study of the tables from the standpoint of the influence of the degree of renal injury on the quantitative output of these bodies in the urine, shows that when the kidney is severely injured, as indicated by a negative elimination of phenolsulphonephthalein and a marked retention of blood urea and creatinin, that the output of acetone and diacetic acid. is reduced and also that the reserve alkali of the blood shows a further depletion. It would appear from these observations that quantitative determinations of ketone bodies in the urine is in no sense a true expression of the disturbance in the acid-base equilibrium of the blood. The observations would furthermore indicate that with the development of a sufficient degree of renal injury the elimination of these bodies is interfered with and their retention may explain the severe depletion in the alkali reserve of the blood which is associated with some types of severe kidney injury.

REPORT ON MICROSCOPIC PATHOLOGY

All of the experiments included in Group 1 were terminated on the sixth day with the object of ascertaining the pathology of the kidney in a large number of animals that were showing the same type of functional response. Kidney tissue was at once removed and fixed in a 10 per cent. solution of liquor formaldehyd, Zenker's fluid and in a corrosive-acetic solution. Frozen sections were made from the liquor formaldehyd fixed tissue and stained for fat with Scharlach R. Sections from the Zenker and corrosive-acetic fixed tissue were stained with hematoxylin and eosin.

The histologic study of this tissue from the thirty-two acutely nephropathic animals has shown the same type of renal injury. The glomerular vessels have been engorged with blood generally obliterating the subcapsular space. In seven of the animals an exudate of amorphous material, with no definite fibrin, was found in the capsular space and slightly compressed the capillary tufts. The exudates have shown a few red blood cells. The intertubular vessels showed a similar engorgement, but no exudate has been observed between the tubules. The vascular tissue of the kidney has shown no other evidence of injury. Fat has not been demonstrated in the glomerular or intertubular vessels. No cellular reaction has been observed in the glomerular vessels. The vascular pathology in all of the animals has consisted in an acute engorgement of the vessels which has varied in severity.

The absence of thrombi in the vessels and the lack of any cellular reaction would argue against the existence of an injury of a degenerative character.

The pathologic response on the part of the kidney, which has been constant in type but which has varied in severity, has consisted in an acute injury to the renal epithelium. Two types of degenerative changes have occurred. The epithelium of the convoluted tubules has
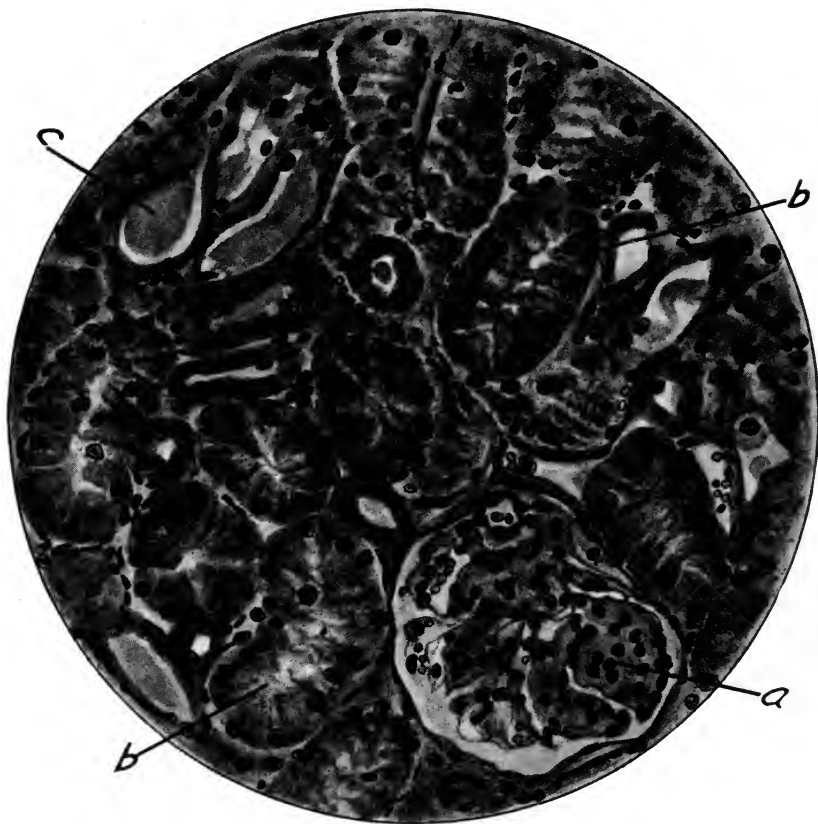
Fig. 1.—Camera lucida drawing, Leitz oc. 2, obj. 6. The figure is from the kidney of the animal of Experiment 4, Table 1, Group I. Following one injection of 4 mg. per kilogram of uranium, the animal developed a severe tubular nephropathy. The output of urine was greatly reduced. The alkali reserve was reduced to 7.7. The phenolsulphonephthalein elimination was negative. There was a retention of both blood urea and creatinin. At A is shown a normal glomerulus. At B are shown the convoluted tubules severely swollen with a beginning necrosis. At C are junctional tubules containing casts.

shown the severest grade of injury. This injury has consisted in an acute swelling and vacuolation of the cells, which is followed by necrosis. Fat occurs in the degenerating epithelium in the form of

numerous fine, dustlike granules. The epithelium of the ascending limb of Henle's loop has shown some swelling but no vacuolation. The cells of this type of epithelium contain a large amount of stainable fat. The fat in this epithelium appears in the form of large droplets which frequently fuse together and obliterate the structure of the cell (Fig. 1).

SUMMARY OF THE ACUTELY NEPHROPATHIC ANIMALS OF GROUP I.

1. The injury induced in the kidney of the dog by one subcutaneous injection of 4 mg. of uranium nitrate per kilogram and extending over a period of six days is essentially a tubular nephropathy. The tubular injury is very largely confined to the convoluted tubule epithelium and to the epithelium of the ascending limb of Henle's loop.

2. The earliest functional disturbance indicative of the development of this injury has consisted in the appearance of albumin in the urine and a reduction in the elimination of phenolsulphonephthalein.

3. Coincident with the appearance of albumin in the urine and the reduction in the elimination of phenolsulphonephthalein there occurs a disturbance in the acid-base equilibrium of the blood, which is indicated by a reduction in the alkali reserve of the blood and a decrease in the tension of alveolar air carbon dioxid.

4. In such acute tubular nephropathies there exists a correlation between the degree of depletion of the alkali reserve of the blood and the elimination of phenolsulphonephthalein.

5. The quantitative output of albumin in the urine is no index of the severity of the renal injury. The output of albumin in the urine may progressively decrease, while the elimination of phenolsulphonephthalein is reduced to a negative quantity.

6. Associated with the reduction in the alkali reserve of the blood, the appearance in the urine of ketone bodies is variable. The quantitative output of these bodies in the urine is not a quantitative expression of the degree of disturbance in the acid-base equilibrium of the blood. With the development of a severe grade of renal injury as indicated by the elimination of phenolsulphonephthalein, the output in the urine of both acetone and diacetic acid is reduced. Associated with this reduced elimination of these bodies there occurs a further disturbance in the acid-base equilibrium of the blood which is indicated by a further depletion in the alkali reserve and a decrease in the tension of carbon dioxid in alveolar air.

7. After the establishment of the renal injury, as indicated by the appearance of albumin in the urine and a reduction in the elimination of phenolsulphonephthalein, there occurs a retention of blood urea and creatinin.

8. The percentage retention of these substances increases with the severity of the injury to the tubular epithelium.

9. The rapidity with which the renal injury develops, the severity of the injury, and the degree of the functional disturbance as indicated by the various functional tests is strikingly influenced by the age of the animal.

10. The older animals show a more severe type of nephropathy and an earlier and more marked functional disturbance than do the young animals.

GROUP II. RECOVERY EXPERIMENTS FROM AN ACUTE RENAL INJURY
DUE TO URANIUM WITH THE PRODUCTION OF A
CHRONIC TYPE OF NEPHROPATHY

Twenty-eight dogs have been employed in this group of experiments. The animals have varied in age from 9 years and 2 months to 9 months. The acute renal injury has been produced in this group of animals in a manner similar to that for the first group. The animals were given subcutaneously one dose of uranium nitrate of 4 mg. per kilogram. The same general technic regarding food and water and the same tests for renal function and for ascertaining the degree of disturbance in the acid-base equilibrium of the blood have been employed in this group of animals as was used for the former group.

Depending on the age of the animals used in this second group of experiments, the animals may be divided into two classes, those animals which show a partial recovery from the acute renal injury and by the processes of repair in the kidney develop a chronic type of nephropathy, and those animals which are unable to further the processes of repair so that a chronic type of renal injury can be produced and so enable the animal to recover partially. The old animals of the group fall in this latter class, which fail to recover. We have been unable to obtain such recovery experiments in animals more than 2 years of age. The younger animals of the group have shown various degrees of recovery. During the course of the uranium intoxication in these animals, the experiments have been terminated at various periods in order to observe the pathologic changes in the kidney at various stages in the functional recovery of the organ from the acute nephropathy. The earliest period for the termination of an experiment has been on the tenth day. The longest period for the duration of an experiment has been ninety-one days. For the sake of reducing the length of the tables in recording the course of these experiments, observations have only been recorded on every other day or in some instances on every fifth day of the experiment. Routine examinations were made, however, every day for the duration of the intoxication.

In order to demonstrate the influence of the age of the animal on the course of the recovery three experiments have been selected from animals of different age periods. Experiment 24, Group 2, Table 5 was carried out in an animal 4 years and 2 months old. Experiment 31,

TABLE 5.—Group II, Experiment 24. Recovery Experiment from Uranium with the Production of a Chronic Nephropathy

Animal: Age, 4 years, 2 months; weight, 15.2 kg.

Day of Exp.	Water in 24 Hrs., C.c.	Ura-nium Nitrate per Kg.	Urine in 24 Hrs., C.c.	Albumin and Casts	Ace-tone, Mg. per 100 C.c.	Dia-cetic Acid, Mg. per 100 C.c.	Blood Urea, Mg. per 100 C.c.	Blood Creat-inin, Mg. per 100 C.c.	Phthal-ein 2 Hrs., per Cent.	R. p. H.	Carbon Dioxid Ten-sion, Mm.
Nor-mal	50.	0	390	0	0	0	18	2.3	84	8.1	45
1	500	4 mg.	915	2 gm. Casts	0	0	59	3.0	20	7.85	35
2	500	0	697	3.6 gm. Casts	1.632	3.265	72	4.31	Trace	7.9	30
4	500	0	587	4 gm. Numerous casts	3.498	2.352	120	4.52	0	7.8	20
6	500	0	184	4 gm. Numerous casts	2.425	2 099	121	5.03	0	7.75	20
8	500	0	100	2 gm. Numerous casts	Not made	Not made	134	5.26	0	7.75	20
10	500	0	0	Not made	Not made	Not made	284	6.18	No urine	7.7	12

TABLE 6.—Group II, Experiment 3. Recovery Experiment from Uranium with the Production of a Chronic Nephropathy

Animal: Age, 1 year, 4 months; weight, 15.9 kg.

Day of Exp.	Water in 24 Hrs., C.c.	Ura-nium Nitrate per Kg.	Urine in 24 Hrs., C.c.	Albumin and Casts	Ace-tone, Mg. per 100 C.c.	Dia-cetic Acid, Mg. per 100 C.c.	Blood Urea, Mg. per 100 C.c.	Blood Creat-inin, Mg. per 100 C.c.	Phthal-ein 2 Hrs., per Cent.	R. p. H.	Carbon Dioxid Ten-sion, Mm.
Nor-mal	500	0	340	0	0	0	12	2.0	73	8.1	43
1	500	4 mg.	626	1.2 gm. Few casts	0	0	16	2.0	61	7.95	38
2	500	0	481	1.1 gm. Casts	1.208	2.755	24	2.0	45	7.95	38
4	500	0	210	0.6 gm. Casts	5.659	7.397	48	2.31	21	7.9	30
6	500	0	230	0.2 gm. Casts	5.995	2.755	70	2.91	Trace	7.9	30
10	500	0	381	0.2 gm. Casts	3.668	4.639	100	3.41	0	7.85	24
14	500	0	503	Trace	2.417	3.442	200	4.281	0	7.85	25
18	500	0	600	0	2.659	4.399	206	4.28	Trace	7.85	25
22	500	0	700	0	2.707	4.303	208	4.28	Trace	7.85	25
26	500	0	794	0	10.782	6.865	218	4.30	10	7.9	32
30	500	0	628	0	9.285	13.581	180	4.32	10	7.9	33
34	500	0	623	Trace Few casts	12.681	16.342	170	4.18	15	7.95	35
38	500	0	346	0	Trace	1.819	148	3.61	15	7.95	35

Group 2, Table 6, in an animal 1 year and 4 months old, while Experiment 8, Group 2, Table 7 was conducted in an animal 9 months old.

A study of the tables of experiments, which are representative of this group of animals, shows a response on the part of the animals

similar in type to that described in detail for the animals of Group 1. It will be noted, as was the case for the former group, that the functional disturbance of the kidney and the change in the acid-base equilibrium of the blood is more rapidly produced and is of greater severity in the old animal of Experiment 24 than it is in the young animal of Experiment 8.   A study of Experiment 24, Table 5, which represents the older group of animals, shows that during the first day of the uranium intoxication there occurred a sudden reduction in the reserve alkali of the blood from 8.1 to 7.95, a reduction in the tension of carbon

TABLE 7.—Group II, Experiment 8. Recovery Experiment from Uranium
with the Production of a Chronic Nephropathy

Animal: Age, 9 months; weight, 13.42 kg.

Day of Exp.	Water in 24 Hrs., C.c.	Uranium Nitrate per Kg.	Urine in 24 Hrs., C.c.	Albumin and Casts	Acetone, Mg. per 100 C.c.	Diacetic Acid, Mg. per 100 C.c.	Blood Urea, Mg. per 100 C.c.	Blood Creatinin, Mg. per 100 C.c.	Phthalein 2 Hrs., per Cent.	R. p. H.	Carbon Dioxid Tension, Mm.
Normal	500	..	605	0	0	0	18	2.03	84	8.1	45
1	500	4 mg.	619	Trace	8.863	2.799	28	2.03	56	8.0	40
2	500	..	300	2.2 gm. Casts	3.416	4.315	59	2.71	Trace	7.95	34
4	500	..	434	9.6 gm. Casts	12.631	13.0	62	2.70	Trace	7.95	35
6	500	..	284	0.4 gm. Casts	9.436	21.321	77	2.70	Trace	7.95	35
8	500	..	475	Trace Few casts	10.796	9.433	177	3.14	0	7.85	23
10	500	..	198	0	9.430	9.963	180	3.14	0	7.75	20
12	500	..	397	0	6.904	8.162	297	4.75	0	7.75	18
16	500	..	511	Trace Casts	6.064	12.498	258	5.31	14	7.8	20
20	500	..	643	Trace Casts	11.942	23.831	183	5.25	24	7.85	25
25	500	..	612	Trace Casts	14.713	21.931	108	4.64	24	7.9	30
30	500	..	450	Trace Casts	16.431	20.820	73	4.50	29	7.9	30
35	500	..	561	Trace Casts	6.994	6.960	56	4.18	35	7.9	30
37	500	..	381	0.25 gm. Casts	8 641	7.932	45	3.75	37	7.95	30
40	500	..	523	0.7 gm. Casts	6.064	10.263	51	3.75	37	7.95	30
45	500	..	525	0.2 gm. Casts	6.064	3.245	61	3.25	36	8.0	40
50	500	..	431	Trace Casts	8.132	4.176	43	2.78	38	8.0	40
60	500	..	732	Trace Casts	7.624	8.315	49	2.76	38	8.0	40

dioxid in alveolar air from 45 to 35 mm., a decrease in the elimination of phenolsulphonephthalein from 84 per cent. to 20 per cent., and the appearance of both albumin and casts in the urine.   In these old and highly susceptible animals there furthermore occurs during the first day of the experiment a retention of both blood urea and creatinin. The blood urea retention is proportionately larger than is the retention of creatinin.   In this susceptible group of old animals there occurs a rapid depletion in the reserve alkali of the blood, the elimination of phenolsulphonephthalein is reduced to zero in four to six days, and

there occurs a progressive retention of blood urea and creatinin. In Experiment 24 the output of urine was decidedly reduced by the sixth day, and by the tenth day the animal was anuric. On this day the reserve alkali of the blood had been depleted to 7.7 and the tension of alveolar air carbon dioxid had been reduced to 12 mm. The animal was semicomatose with an atypical type of air hunger breathing. Blood urea showed a retention of 284 mg., as compared with the normal of 18 mg. and blood creatinin a retention of 6.18 mg. in contrast with the normal of 2.3 mg.

The pathologic study of the kidneys of these old animals that have shown no attempt to reestablish a normal acid-base equilibrium of the blood and, furthermore, no indication of a restoration of renal function, have failed to show any evidence of reparative changes of a constructive character. Mitotic figures have not been observed in the damaged renal epithelium, and no other evidence of regeneration has been obtained. The cells of the convoluted tubules in the uranium nephropathies of such duration are largely necrotic. Vacuolation and the associated swelling are marked, so that in many of the tubules the lumen has become obliterated by the edematous cells. These cells contain a large amount of fat. The cells of the ascending limb of Henle's loop show a similar type of reaction. The necrosis is not so extensive. In such a prolonged injury from uranium the vascular tissue of the kidney becomes involved in the reaction. In addition to the acute engorgement of the glomerular vessels which was noted as the essential change in the vascular pathology during the early stage of a uranium nephropathy, in these injuries of longer duration thrombi have been observed in the tuft of capillaries. An exudate containing fibrin has been noted in the subcapsular space adhering to the capsular epithelium. In such an exudate as well as in the thrombi of the capillaries, endothelial leukocytes have been active. The capsular epithelium is swollen and in such injured cells mitotic figures have been observed. The acute nephropathy of ten days or more duration in these old and susceptible animals is not only characterized by an injury to the epithelium of the tubules, but by an injury to the glomeruli. Regenerative changes do not occur in the tubules of such animals and there is no attempt at a restoration of renal function.

A study of Experiments 3 and 8, Tables 6 and 7, which represent typical experiments in the younger animals of the group, show a similar type of response from uranium as did the older animals. The intoxication in the younger animals, however, as is indicated by the disturbance in the acid-base equilibrium of the blood and by the various tests for renal function, is not so abrupt in its onset and the disturbance is not so marked early in the experiments. During the period of the acute kidney injury, before there occurs any evidence of a come-back

on the part of the kidney, a marked depletion in the alkali reserve of the blood develops and renal function is seriously interfered with. In Experiment 3, by the tenth day of the uranium intoxication the reserve alkali of the blood had been depleted to 7.85, the output of phenolsulphonephthalein was reduced to zero, there was a retention of blood creatinin of 3.41 mg. and of blood urea of 100 mg. With this degree of disturbance in the acid-base equilibrium of the blood and in renal function the urine showed only 0.2 gm. of albumin per liter. At this period of the experiment the urine contained both acetone and diacetic acid. It will be noted, however, that these bodies were present in less amount than they were early in the experiment when renal function was not so severely interfered with, and at which time the kidney was still able to secrete these bodies.

In Experiment 8, Table 7, the same type of injury is induced. In this animal, on the twelfth day of the uranium intoxication, the reserve alkali of the blood was depleted to 7.75, and the tension of alveolar air carbon dioxid was reduced to 18 mm. Prior to this on the eighth day of the experiment the elimination of phenolsulphonephthalein had reached the zero point and remained negative for four days. On the twelfth day the injury to the kidney was furthermore shown by a creatinin retention of 4.75 mg. and a retention of blood urea of 297 mg. Both acetone and diacetic acid were present in the urine, but present in a smaller percentage than was the case earlier in the experiment when all of the tests showed a higher grade of renal function. A continuation of the study of Experiments 3 and 8, which were conducted in young dogs, shows that from the fourteenth to the eighteenth days of the nephropathy the injury to the kidney has reached its height. From this period to the termination of the experiments there is an attempt on the part of the kidney to reestablish some degree of function.

The pathologic studies have shown that commencing with this period of the experiment there is histological evidence of changes of repair and regeneration of renal epithelium. The first evidence of an improvement in renal function has consisted in the reappearance of phenolsulphonephthalein in the urine. In Experiment 3 the dye first appeared on the eighteenth day, while in Experiment 8 the appearance was first noted on the fourteenth day. For the first two to four days, after the reappearance of phenolsulphonephthalein, the output has been so small as to render difficult its determination. Following this period the output has increased so that in from four to eight days the elimination has increased from 10 to 14 per cent. With the reappearance of phenolsulphonephthalein in the urine no immediate change takes place in the retention of urea and creatinin, and neither is there any immediate change in the degree of depletion of the alkali reserve of the blood. In from four to six days after the first appearance of

phenolsulphonephthalein in the urine, at which time the animals were eliminating from 10 to 24 per cent. of the dye, there has occurred a beginning increase in the alkali reserve of the blood.

At the same time that this change takes place in the blood, there has occurred an increase in the output in the urine of both acetone and diacetic acid. This observation would tend to show that a part of the disturbance in the acid-base equilibrium of the blood induced by uranium is due to a retention of acid bodies. Furthermore, that with an improvement in renal function as was indicated by the elimination of phenolsulphonephthalein, certain bodies which the kidney has been unable to secrete, for instance acetone and diacetic acid, are now eliminated, and with their removal there occurs a beginning reestablishment of the acid-base equilibrium of the blood. Experiment 8 very clearly illustrates these changes. For four days after the kidneys were eliminating from 14 to 24 per cent. of phenolsulphonephthalein there was no change in the alkali reserve of the blood. At the end of this period the reserve alkali increased from 7.8 to 7.9 and the tension of carbon dioxid in alveolar air increased from 20 to 30 mm. During this stage of the experiment the elimination of acetone increased from 6.064 to 14.713 mg. per hundred c.c. of urine, and the elimination of diacetic acid has increased from 12.498 to 21.931 mg. per hundred c.c.

A study of Experiments 3 and 8 furthermore shows that the threshold in the nephropathic kidney for the elimination of urea and creatinin is higher than it is for phenolsulphonephthalein. In Experiment 3 the retention of both urea and creatinin continued for four and six days, respectively, after the elimination of phenolsulphonephthalein had reached 10 per cent. Following this period there first occurred a decrease in the retention of blood urea and four days later the retention of creatinin began to decrease.

A further study of these experiments shows that following the commencement of the period of improvement in renal function there occurs a gradual increase in the elimination of phenolsulphonephthalein, a decrease in the retention of urea and creatinin, and an increase in the reserve alkali of the blood to such an extent that the acid-base equilibrium of the blood is either restored or brought near the point of normality. In nine of the animals used in the group the functional capacity of the kidney underwent such an improvement during the period of recovery that between the eightieth and ninetieth days of the experiment the acid-base equilibrium of the blood had been restored to the normal. In the remaining animals of the group there occurred an increase in the reserve alkali, but the normal acid-base equilibrium was not reestablished.

The period of recovery of the kidney from the acute nephropathy with a partial return of renal function during the development of the

chronic nephropathy is well shown in Experiment 8, Table 7. At the height of the acute injury, on the twelfth day of the experiment, the reserve alkali was reduced to 7.75. In a two hour period there was no elimination of phenolsulphonephthalein. The blood showed a retention of 297 mg. of urea and a creatinin retention of 4.75 mg. At the termination of the experiment on the sixtieth day the reserve alkali had increased to 8.0, and the tension of carbon dioxid in alveolar air to 40 mm. There was an elimination of phenolsulphonephthalein of 38 per cent. in two hours. The urea retention had been reduced to 49 mg. and the creatinin retention had decreased to 2.76 mg. A study of this experiment, and the following observation, shows even more clearly in those animals that are able to restore their acid-base equilibrium to the normal that the elimination of phenolsulphonephthalein does not show a correlation in quantitative output with the change towards the normal in the alkali reserve of the blood. The elimination of phenolsulphonephthalein was in no instance over 40 per cent. in the nine animals that succeeded in reestablishing their normal acid-base equilibrium. An animal with a severe grade of chronic nephropathy may have a normal alkali reserve of the blood and a normal tension of carbon dioxid in alveolar air. As will be shown later in Group III, such a finding is no expression of the stability of the acid-base equilibrium in a given animal. Determinations of the alkali reserve of the blood can in no sense be employed as an index of renal function or as an index of the ability of the kidney to withstand injury.

THE PATHOLOGY OF THE KIDNEY IN THOSE ANIMALS OF GROUP II THAT HAVE RECOVERED FROM THE ACUTE RENAL INJURY WITH THE DEVELOPMENT OF A CHRONIC NEPHROPATHY

The pathologic changes observed in the kidneys of this group of animals have depended on the stage of recovery at which the kidney tissue was obtained. The earliest evidence of repair in the kidney has been found between the eighth and fifteenth days of the intoxication. It will be recalled in this connection that the earliest indication of any functional restoration developed between the fourteenth and eighteenth day and consisted in the reappearance of phenolsulphonephthalein in the urine. The first evidence of repair in the kidney has consisted in a beginning regeneration of tubular epithelium. This first occurs in the terminal portion of the proximal convoluted tubule and in the upper portion of the descending limb of Henle's loop. The regeneration of cells occurs by a process of indirect cell division of the epithelium in those portions of the tubule that have not been too severely injured. The newly formed cells are large and vesicular with hyperchromatic

nuclei. Frequently the cell boundaries are not clearly differentiated. This gives rise to the formation in some tubules of a syncytial-like layer of epithelium which grows into the severely damaged convoluted tubule. At a later period the syncytial cyptoplasmic mass differentiates into cells. At this early period of the renal injury there has been found an early cellular intertubular fibrosis. The glomerular vessels are invaded with fibroblasts and endothelial leukocytes and the capsular epithelium is hyperplastic.

In experiments that were terminated later in the period of recovery, between the twentieth and thirtieth day, the changes of repair have shown an increase. Many of the convoluted tubules are lined by the newly formed epithelium, which, however, has become changed in character. The cells which at first were large and vesicular have flattened out so that the tubules are lined by regenerated cells of a flattened type with a small amount of surrounding cytoplasm. The nuclei are large in proportion to the cytoplasm, and frequently project on the free margin of the cell. These cells are less specialized in structure than are the normal cells of the convoluted tubule. At this stage of repair in the kidney, the intertubular connective tissue has become more fibrous in character. In the glomeruli there is an early laying down of connective tissue which mats together the capillary loops and the walls of the capillaries become thickened. Between the capillary tufts and the capsule, the laying down of young connective tissue results in the formation of adhesions. The capsules show an increase in spindle-shaped cells and later become thickened. Around the glomeruli there is an early cellular periglomerular fibrosis.

A review of Experiments 3 and 8 indicates that at this stage of the experiments, between the twentieth and thirtieth days, an improvement in the functional response of the kidney occurs which is indicated by a further increase in the elimination of phenolsulphonephthalein, which may be as much as 29 per cent. There has occurred a decrease in the retention of blood urea and creatinin, an increase in the elimination of ketone bodies and an increase in the alkali reserve of the blood. The following observation is significant and of great importance that at this stage of the experiment when the tubular epithelium is being replaced, but when the glomeruli are being permanently damaged by the formation of fibrous tissue which obliterates the capillaries and causes a thickening of the capsule, there is a progressive increase in the functional capacity of the kidney. From this observation it appears only just to infer that the epithelial tissue of the kidney is of more functional value than is the vascular tissue.

The pathologic study of the kidney of animals late in the recovery from the acute renal injury when the chronic nephropathy has been definitely established shows a continuation of those processes of repair

previously described. The replacement of a flattened and atypical type of epithelium in the convoluted tubules continues. Many of the tubules show the original convoluted tubule epithelium in various stages of degeneration, while other tubules show a regeneration of this type of cell. Such damaged cells show much stainable fat. The intertubular connective tissue, though not marked in amount, has changed from a cellular form to connective tissue made up of fibers and spindle-shaped cells. In the glomeruli the amount of connective tissue in the
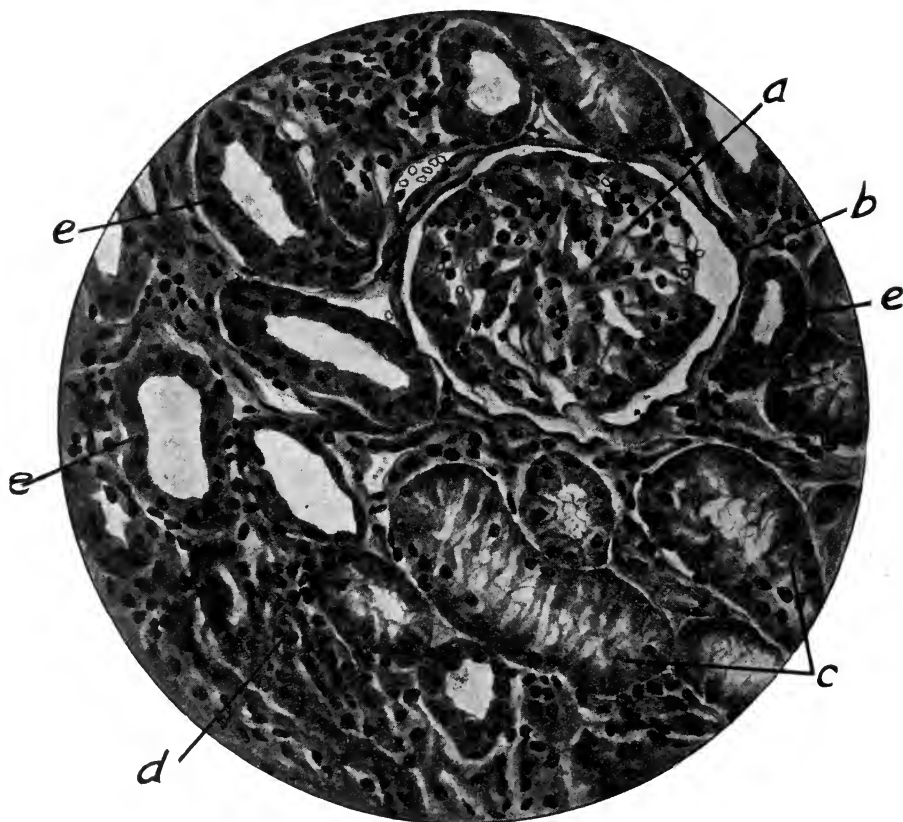
Fig. 2.—Camera lucida drawing, Leitz oc. 2, obj. 6. The figure is from the kidney of the animal of Experiment 8, Table 7, Group 2. The animal has partially recovered from an acute kidney injury from uranium with the development of a chronic nephropathy. The output of urine was normal. The urine contained a trace of albumin and casts. The reserve alkali was 8, phenol-sulphonephthalein elimination 38 per cent. There was a slight retention of blood urea and creatinin. At A is shown a glomerulus with the capillaries matted together and an increase in connective tissue nuclei. At B is shown an early thickening of the capsule. At C are shown two of the original convoluted tubules that are undergoing degeneration. At D the intertubular connective tissue is hyperplastic. At E are shown tubules lined by regenerated, flattened, atypical and less specialized epithelium.

form of fibers has increased. Many of the capillary loops have become obliterated, and fibrous adhesions have formed between the capillary tufts and the capsule. The capillaries show a decrease in fibroblasts, but an increase in thickness from the laying down of connective tissue fibers. The periglomerular fibrosis at this stage of the injury consists of newly-formed connective tissue fibers, rich in fibroblasts.

The terminal pathology resulting from the repair of the acute kidney injury leads to the development of a chronic type of nephropathy, which is characterized by a replacement in the damaged tubules of a flattened and less specialized type of epithelium and by a permanent injury to the glomeruli through the formation of connective tissue which is both intracapillary and capsular in location (Fig. 2).

SUMMARY OF THE ANIMALS OF GROUP II, WHICH RECOVERED FROM THE ACUTE RENAL INJURY WITH THE DEVELOPMENT OF A CHRONIC NEPHROPATHY

1. The ability of the members of this group to recover has depended upon the age of the animal. The older animals become anuric, develop an atypical type of air hunger breathing and die either in coma or in a period of convulsions which may precede the coma. The younger animals of the group, after a period of severe renal injury, have recovered with the development of a chronic nephropathy.

2. The earliest evidence of a beginning recovery has consisted in the reappearance of phenolsulphonephthalein in the urine. As the percentage output of the dye increases, there occurs an increase in the alkali reserve of the blood, and an associated increase in the tension of carbon dioxid in alveolar air. There is an attempt to reestablish the normal acid-base equilibrium of the blood. In nine of the animals the acid-base equilibrium has been restored to the normal.

3. Associated with the above evidence of an improvement in renal function there occurs an increase in the output of both acetone and diacetic acid in the urine.

4. After the kidney has established a certain degree of functional improvement there occurs, first, a decrease in the retention of blood urea, and second, a decrease in the retention of creatinin.

5. At the termination of all of the experiments, including those animals in which the alkali reserve of the blood was restored to the normal, there existed marked evidence of renal injury, as was shown by the low output of phenolsulphonephthalein and some degree of retention of urea and creatinin.

6. The kidneys of those animals which have recovered to the point of establishing a chronic nephropathy, have shown histologically a regeneration of tubular epithelium, which is atypical and the establish-

ment of chronic changes in the glomeruli which result in an obliteration and thickening of the capillary loops, a thickening of the capsule and the formation of adhesions between the capsule and the capillary tufts.

GROUP III. NATURALLY NEPHROPATHIC ANIMALS IN WHICH AN ACUTE
RENAL INJURY HAS BEEN SUPERIMPOSED ON THE CHRONIC
PATHOLOGY BY URANIUM OR MERCURIC CHLORID

Forty-five animals have been studied in this group of experiments. The course of four of the experiments which have been selected as representative of the group is detailed in Tables 8, 9, 10 and 11. Following a period of study, two days of which is recorded in the tables, the animals were rendered acutely nephropathic by either uranium or mercuric chlorid. By such a technic an acute renal injury has been superimposed on the chronic injury. The course of the nephropathy is detailed in the tables until the termination of the experiment.

A study of these tables shows that the urine of all the animals contained a trace of albumin and casts. The animals were freely diuretic. The daily output of urine varied from 471 to 1,141 c.c. The reserve alkali has varied between 8.0 to 8.1. The tension of alveolar air carbon dioxid has shown a correlation with this finding, and has varied between 38 to 42 mm. With the present interest which is being shown both in the laboratory and the clinic in studies of the acid-base equilibrium of the blood in the various nephropathies, the observation just made is of importance. Animals with certain types of chronic kidney injury may have a normal reserve alkali of the blood. In all of the animals the output of phenolsulphonephthalein has been low. The elimination has varied between a maximum output of 53 per cent. and a minimum output of 33 per cent. The findings in this group of naturally nephropathic animals in so far as the reserve alkali of the blood and the elimination of phenolsulphonephthalein is concerned show a close resemblance to the observations made in the animals of Group II that recovered from an acute kidney injury with the development of a chronic nephropathy. The tables of experiments show furthermore that in these animals with a chronic naturally acquired nephropathy, even with a phenolsulphonephthalein elimination as low as 48 per cent., there may be no marked retention of either blood urea or creatinin. The blood urea in these animals has varied between 19 to 22 mg., and the creatinin between 2.0 to 2.31 mg. From these observations it is clear that in the dog a chronic nephropathy may exist with no evidence of impaired renal function other than appearance in the urine of a trace of albumin with casts and a persistently low output of phenolsulphonephthalein.

Six animals with such functional findings have been killed and the pathology of the kidney studied. The histological changes in the

kidneys of these animals have been similar to those previously described in another paper.[7] The chronic pathology is very largely confined to the glomeruli. The glomeruli show both intracapillary and capsular changes. The tufts of capillaries are infiltrated with fibroblasts. The

TABLE 8.—GROUP III, EXPERIMENT 16. NATURALLY NEPHROPATHIC ANIMAL.
ACUTE KIDNEY INJURY FROM URANIUM

Animal: Age, 8 to 10 years.

Day of Exp.	Water in 24 Hrs., C.c.	Ne-phro-toxic Agent	Urine in 24 Hrs., C.c.	Albumin and Casts	Ace-tone, Mg. per 100 C.c.	Dia-cetic Acid, Mg. per 100 C.c.	Blood Urea, Mg. per 100 C.c	Blood Creat-inin, Mg. per 100 C.c.	Phthal-ein 2 Hrs., per Cent.	R. p. H	Carbon Dioxid Ten-sion, Mm.
1	500	0	595	Trace Occasional cast	0	0	21	2.31	49	8.0	40
2	500	0	742	Trace Occasional cast	0	0	18	2.10	51	8.0	40
3	500	4 mg. ura-nium per kg.	618	3.2 gm. Casts very numerous	0	0	18	2.14	Trace	7.9	30
4	500	0	42 later anuric	4.0 gm. Casts very numerous	Present	Present	48	4.00	0	7.85	25
5	500	0	0	Not made	Not made	Not made	72	4.75	0	7.7	14

TABLE 9.—GROUP III, EXPERIMENT 4. NATURALLY NEPHROPATHIC ANIMAL.
ACUTE KIDNEY INJURY FROM URANIUM

Animal: Age, 7 years, 2 months.

Day of Exp.	Water in 24 Hrs., C.c.	Ne-phro-toxic Agent	Urine in 24 Hrs., C.c.	Albumin and Casts	Ace-tone, Mg. per 100 C.c.	Dia-cetic Acid, Mg. per 100 C.c.	Blood Urea, Mg. per 100 C.c	Blood Creat-inin, Mg. per 100 C.c.	Phthal-ein 2 Hrs., per Cent.	R. p. H.	Carbon Dioxid Ten-sion, Mm.
1	500	0	471	Trace Occasional cast	0	0	19	2.0	45	8.1	42
2	500	0	1141	Trace Occasional cast	0	0	17	2.5	41	8.05	42
3	500	4 mg. ura-nium per kg.	760	1.3 gm. Numerous casts	5.173	1.672	28	2.59	Trace	7.9	30
4	500	0	419	4.0 gm. Numerous casts	0	0	40	2.70	0	7.8	22
5	500	0	158	3.6 gm. Numerous casts	0	0	78	3.74	0	7.75	15
6	500	0	0 Anuric	Not made	Not made	Not made	121	5.32	0	7.7	10

capillary walls are thickened from a laying down of intercapillary connective tissue. Many of the capillary loops are obliterated. The capsular epithelium is frequently hyperplastic and the capsule is rich in fibroblasts and thickened by fibrous tissue. A periglomerular fibrosis has frequently been observed. The tubular epithelium is histologically well preserved. Many of the convoluted tubules appear normal but in

such epithelium fat can be constantly demonstrated by Scharlach R. In other convoluted tubules the epithelium is of the flattened, atypical, regenerated type, which has been previously discussed. The cells of the ascending limb of Henle's loop contain fat. In these naturally

TABLE 10.—Group III, Experiment 22. Naturally Nephropathic Animal. Acute Kidney Injury from Mercuric Chlorid

Animal: Age, 3 years, 7 months.

Day of Exp.	Water in 24 Hrs., C.c.	Ne-phrotoxic Agent	Urine in 24 Hrs., C.c.	Albumin and Casts	Ace-tone, Mg. per 100 C.c.	Dia-cetic Acid, Mg. per 100 C.c.	Blood Urea, Mg. per 100 C.c.	Blood Creat-inin, Mg. per 100 C.c.	Phthal-ein 2 Hrs., per Cent.	R. p. H.	Carbon Dioxid Tension, Mm.
1	500	0	1141	Trace Occasional cast	0	0	21	2.0	48	8.0	38
2	500	0	740	0.5 gm. Occasional cast	0	0	30	2.0	61	8.0	40
3	500	15 mg. mercuric chlorid per kg.	150	1.25 gm. Occasional cast	0	0	34	2.10	12	7.8	28
4	500	0	81	1.5 gm. Numerous casts	0	0	42	2.75	0	7.7	10
5	500 vomited	0	0 Anuric	Not made	Not made	Not made	74	4.68	0	7.65	10 (—)

TABLE 11.—Group III, Experiment 11. Naturally Nephropathic Animal. Acute Kidney Injury from Mercuric Chlorid

Animal: Age, 4 years, 2 months.

Day of Exp.	Water in 24 Hrs., C.c.	Ne-phrotoxic Agent	Urine in 24 Hrs., C.c.	Albumin and Casts	Ace-tone, Mg. per 100 C.c.	Dia-cetic Acid, Mg. per 100 C.c.	Blood Urea, Mg. per 100 C.c.	Blood Creat-inin, Mg. per 100 C.c.	Phthal-ein 2 Hrs., per Cent.	R. p. H.	Carbon Dioxid Tension, Mm.
1	500	0	712	Trace No casts	0	0	22	2.15	53	8.0	40
2	500	0	405	0	0	0	18	2.0	51	8.0	40
3	500	0	1142	0	0	0	24	2.10	33	8.0	40
4	500	15 mg. mercuric chlorid per kg.	714	Trace Occasional case	0	0	23	2.0	12	8.0	40
5	500	0	105	0.25 gm. Occasional cast	0	0	41	3.15	0	7.85	25
6	500	0	0	Not made	Not made	Not made	74	4.25	0	7.8	25
7	500 vomited	0	0	Not made	Not made	Not made	112	4.30	0	7.8	23
8	500 vomited	0	0	Not made	Not made	Not made	184	5.05	0	7.75	10

nephropathic animals with the pathologic changes in the kidney very largely confined to the glomeruli, the functional response may be normal with the exception of the presence of albumin in the urine and the low output of phenolsulphonephthalein (Fig. 3).

The further study of the group of naturally nephropathic animals has consisted in producing an acute nephropathy with either uranium in one dose given subcutaneously of 4 mg. per kilogram, or by employing mercuric chlorid in one dose of 15 mg. per kilogram. The mercury was given to the animals by a stomach tube after they had been par-
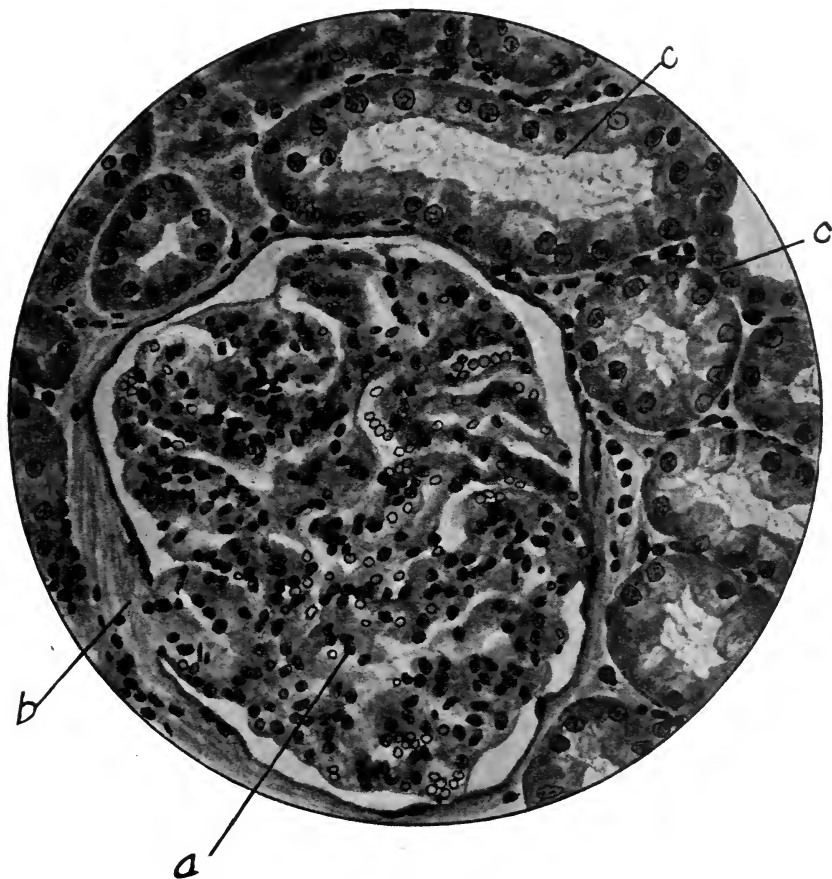
Fig. 3.—Camera lucida drawing, Leitz oc. 2, obj. 6. The figure is from the kidney of one of six naturally nephropathic animals of Group III that were killed after a period of study and before an acute kidney injury was produced by either uranium or mercuric chlorid. The animal had an advanced chronic glomerulonephropathy with but little injury to the tubular epithelium. The daily output of urine was normal. The urine contained a trace of albumin and rarely a hyaline cast. The reserve alkali was 8. The elimination of phenolsulphonephthalein was 49 per cent. There was no retention of either blood urea or creatinin. At A is seen a very large glomerulus with capillary loops thickened and matted together. At B is shown the thickening of the capsule and an adhesion between the capsule and the glomerular tuft. At C are shown convoluted tubules well preserved histologically. There is but slight granulation of the cytoplasm. The nuclei stain well.

tially narcotized by morphin. In a recent paper [19] it has been shown
that mercuric chlorid in such a dose produces an acute epithelial injury
to the kidney and that this injury is associated with a rapid reduction
in the reserve alkali of the blood.

A study of the four tables of experiments representing this group
shows that on the day following the use of either one of these nephro-
toxic agents, there occurs a sharp decrease in the output of urine, and
that the amount of albumin in the urine and the number of casts shows
an increase. Associated with this change in the urine there occurs a
rapid depletion in the alkali reserve of the blood and a marked reduc-
tion in the elimination of phenolsulphonephthalein. In the animal of
Experiment 16 that received uranium, the output of urine was reduced
on the first day from 742 to 618 c.c., and the albumin increased from
a mere trace to 3.2 gm. per liter. The reserve alkali was reduced from
8.0 to 7.9 and the elimination of phenolsulphonephthalein from 51 per
cent. to a trace which could not be determined. In the animal of
Experiment 22, that received mercuric chlorid, the output of urine was
reduced during the first day from 740 to 150 c.c., and the amount of
albumin in the urine increased from 0.25 gm. to 1.25 gm. per liter. In
this same period the reserve alkali of the blood was reduced from
8.0 to 7.8 and the elimination of phenolsulphonephthalein from 61 to
12 per cent. By the second day of the acute renal injury there had
occurred a retention of both urea and creatinin. In the animal of
Experiment 22 that received mercuric chlorid the same type of response
occurred, though to a less marked extent. During the remaining one
to four days of these experiments there occurs a continuation of these
functional changes and a further disturbance in the acid-base equilib-
rium of the blood. By the second or the third day all of the animals
had become anuric and remained anuric until the termination of the
experiments.

The experiments were terminated on the third to the fifth day
following the use of the acutely acting nephrotoxic agent. During this
period the reserve alkali of the blood was progressively depleted until
such low readings as 7.7 to 7.65 were obtained in the various experi-
ments. There was an associated decrease in the tension of alveolar air
carbon dioxid. The elimination of phenolsulphonephthalein was early
in the experiments reduced to zero and remained negative on the suc-
ceeding days. The retention of blood urea and creatinin showed a pro-
gressive increase.

At the termination of the experiments kidney tissue was obtained
for histologic study. The vascular pathology of the kidney in these

19. MacNider, William deB.: A Study of Acute Mercuric Chlorid Intoxi-
cations in the Dog, with Special Reference to the Kidney Injury, J. Exper.
Med. **27**:519, 1918.

animals with a naturally acquired chronic nephropathy that have received either uranium or mercuric chlorid, has shown no evidence of an acute injury other than the engorgement of the glomerular vessels. The vascular pathology is essentially that of a chronic glomerulo-nephropathy. The acute changes in the kidney that have been super-imposed on the chronic pathology consist in an acute injury to the
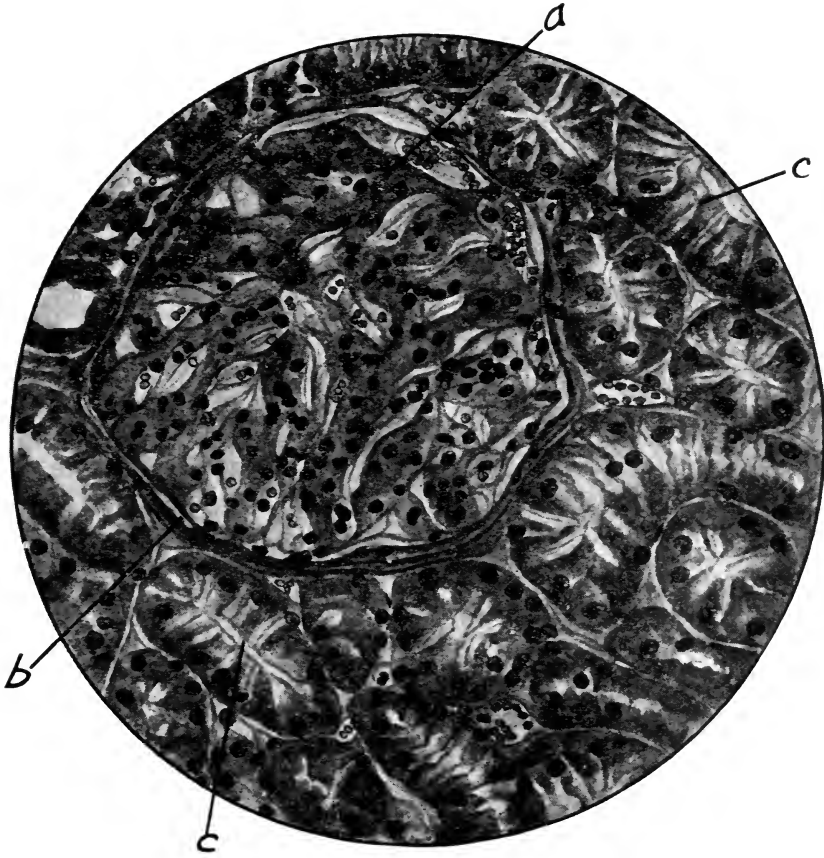
Fig. 4.—Camera lucida drawing, Leitz oc. 2, obj. 6. The figure is from the kidney of Experiment 11, Table 11, Group III. The animals had a naturally acquired chronic glomerulonephropathy. An acute tubular nephropathy was superimposed on the chronic pathology by mercuric chlorid. The animal became anuric on the third day following the use of mercuric chlorid. The reserve alkali of the blood was reduced to 7.7. The phenolsulphonephthalein elimination in a two hour period was negative. There was a retention of blood urea of 184 mg. and of creatinin of 5.05 mg. per 100 c.c. of blood. At A is shown a large glomerulus. The capillary walls are thickened and matted together. The glomerulus contains numerous connective tissue nuclei. At B is shown an early thickening of the capsule of the glomerulus. At C are shown convoluted tubules the epithelium of which is severely swollen and vacuolated and beginning to undergo necrosis.

tubular epithelium, and especially of the proximal convoluted tubules and the ascending limb of Henle's loop. These changes consist in an acute swelling, with granulation and vacuolation of the cells which is rapidly followed by necrosis. The convoluted tubule epithelium has shown a moderate amount of fat, while the epithelium of the ascending limb of Henle's loop has contained fat in a much larger amount. The acute injury produced in the naturally nephropathic kidney by the use of uranium or mercuric chlorid is confined to the tubular epithelium. The functional response of the kidney associated with this injury is characterized by a rapid reduction in the output of urine and an increase in the amount of albumin and number of casts. At the same time that this change occurs, the reserve alkali of the blood shows a marked depletion and the elimination of phenolsulphonephthalein is rapidly reduced to zero. Following this functional disturbance a rapid retention of both blood urea and creatinin takes place which increases until the termination of the experiment. In such naturally nephropathic animals with an acute tubular injury there has been no histological evidence in the kidney, and no functional response to indicate a reestablishment of kidney function (Fig. 4).

SUMMARY FOR THE NATURALLY NEPHROPATHIC ANIMALS OF GROUP III
IN WHICH AN ACUTE KIDNEY INJURY WAS SUPERIMPOSED
ON THE CHRONIC INJURY BY URANIUM OR
MERCURIC CHLORID

1. The type of chronic naturally acquired nephropathy which has been observed in the dog is characterized anatomically by an injury to the glomerulus which is out of proportion to the severity of the changes in the renal epithelium. A similar observation has been made by Stengel, Austin and Jonas [8] for certain nephropathies in human material.

2. The functional response of the kidney in this type of injury is characterized by a low phenolsulphonephthalein output and by the presence in the urine of a small amount of albumin. Casts have been constantly present.

3. In such nephropathies with the injury very largely confined to the glomeruli and with an elimination of phenolsulphonephthalein which has varied between 53 to 38 per cent. there has not occurred a retention of either blood urea or creatinin. From this observation it would appear that for this type of chronic vascular injury the phenolsulphonephthalein elimination test is of more value than are the retention tests of blood urea and creatinin. It would furthermore appear that the injury to the kidney as indicated by the elimination of phenol-

sulphonephthalein must be of a severe type before kidney function becomes sufficiently impaired to indicate the injury by a retention of these substances.

4. Naturally nephropathic animals with but slight histologic evidence of injury to the tubular epithelium, but with a marked glomerulonephropathy, may be able to maintain a normal acid-base equilibrium of the blood as is indicated by the reserve alkali of the blood and the tension of carbon dioxid in alveolar air. Such an observation is, however, no index of the stability of the acid-base equilibrium. When such animals are subjected to the action of agents as uranium or mercuric chlorid that are known to disturb the acid-base equilibrium in normal animals, in these naturally nephropathic animals the depletion of the blood of its alkali reserve occurs more suddenly and to a greater extent than is the case in normal animals. The acid-base equilibrium in a naturally nephropathic animal may be maintained at the point of normality, but when the mechanism which effects such a maintenance is subjected to the strain of maintaining it against an accumulation of acid ions, its lack of stability is shown by a rapid reduction in the alkali reserve with the development of an acid intoxication.

5. Following the use of either uranium or mercuric chlorid in these naturally nephropathic animals there occurs a rapid reduction in the alkali reserve of the blood and a marked reduction in the ability of the kidney to eliminate phenolsulphonephthalein. Within twenty-four hours the elimination of the dye has been reduced to a trace, or it has failed to appear in the urine. Associated with these·changes the output of urine is sharply reduced and the amount of albumin in the urine is increased. Later during the course of the acute kidney injury, from one to three days after the initial reduction in the output of phenolsulphonephthalein, there develops a rapid retention of both blood urea and creatinin. These animals become rapidly anuric. During the development of the anuria, the reserve alkali of the blood continues to be depleted, no phenolsulphonephthalein appears in the urine, and the retention of blood urea and creatinin show a progressive increase.

6. At the termination of such experiments the histologic study of the kidneys has shown the essential pathology which develops in the naturally nephropathic animals from the use of uranium or mercuric chlorid to consist in an acute tubular injury without any acute injury having been superimposed on the chronic glomerular pathology. From this observation the deduction appears permissible that the functional capacity of the naturally nephropathic kidney, as indicated by the ability of such a kidney to form urine and to eliminate phenolsulphonephthalein, urea and creatinin is more dependent on the histologic preservation of the renal epithelium than it is on the preservation of the normal structure of the glomeruli.

GENERAL DISCUSSION

The foregoing study has been concerned with two main points: The value of certain tests for renal function in definite types of acute and chronic renal disease, and of the influence of the disturbance in the acid-base equilibrium of the blood which occurs in these nephropathies on the pathology of the kidney and on its functional response.

In our earlier studies on renal function, tests other than those employed in the present investigation were made use of. These tests included a study of the elimination of sodium chlorid, lactose and potassium iodid as first used by Schlayer and Takayasu[20] and later employed by Rowntree, Fitz and Geraghty.[21] In addition to these tests, studies of renal function were conducted by employing Ambard's coefficient for urea elimination as modified by McLean[22] and extensively used in the studies of Mosenthal and Sclater.[23] In our later studies, including those found in this paper, these tests have not been employed. In our experience, the elimination of sodium chlorid, lactose and potassium iodid have been so variable, even in nephropathies in which one fairly definite type of injury was found to exist, that their value has become questionable. The use of Ambard's coefficient has been discontinued as a functional test, for it gives less accurate information of the ability of the kidney to secrete a substance than does the phenolsulphonephthalein test. Furthermore, as has been recently pointed out by Addis and Watanabe,[24] the rate of urea excretion in man varies in a manner which cannot be explained by the concentration of urea in the blood and urine. For these reasons, we have confined our observations to the use of the phenolsulphonephthalein test as an index of the immediate functional capacity of the kidney and have used estimations of blood urea and creatinin as indices of retention.

These tests have been employed in animals with a naturally acquired or experimentally produced nephropathy. The experiments were terminated at different periods during the renal injury and observa-

20. Schlayer and Takayasu: Untersuchung über die Funktion kranker Nieren, Deutsch. Arch. f. klin. Med. **93**:17, 1909.

21. Rowntree, L. G., Fitz, R., and Geraghty, J. T.: The Effects of Experimental Chronic Passive Congestion on Renal Function, Arch. Int. Med. **11**: 121, 1913.

22. McLean, Franklin C.: The Mechanism of Urea Retention in Nephritis, Studies from the Rockefeller Institute for Medical Research, **28**:549, 1918. Nephritis from the Standpoint of Urea Excretion, Studies from the Rockefeller Institute for Medical Research, **28**:569, 1918.

23. Mosenthal, Herman O., and Sclater, Lewis D.: A Comparative Study of Tests for Renal Function, J. A. M. A. **67**:933 (Sept. 23) 1916.

24. Addis, Thomas, and Watanabe, C. K.: Rate of Urea Excretion. A Criticism of Ambard's and Weill's Laws of Urea Excretion, J. Biol. Chem. **24**:203, 1916.

tions made on the functional capacity of the kidney in connection with a definite pathologic state as found in the kidney. In an animal with a pure tubular injury as is produced by uranium in the early days of the intoxication, the first functional disturbance on the part of the kidney consists in a reduction in the elimination of phenolsulphonephthalein, the appearance of albumin in the urine and associated with these functional changes there is a reduction in the reserve alkali of the blood. There is a definite relationship between the injury to the tubular epithelium, the reduction in the elimination of phenolsulphonephthalein and the appearance of albumin and casts in the urine. At this stage of such an experiment there is no glomerular injury. At this early period of such experiments, it is difficult to state just what the relationship is from the standpoint of causation, between the reduction in the reserve alkali of the blood and the establishment of the injury to the tubular epithelium. By the methods which have been employed in this study, our observation has been that the reduction in the reserve alkali of the blood and the development of the tubular injury either occur at the same time or the depletion of the alkali reserve of the blood occurs prior to the development of the tubular injury, as is shown by the elimination of phenolsulphonephthalein, and the appearance of albumin and casts in the urine. This early change in the acid-base equilibrium of the blood should not be looked on as a disturbance due to retention from an injury to the kidney. The naturally nephropathic animals have shown that the acid-base equilibrium may be normal and yet there may be a decrease in the elimination of phenolsulphonephthalein which is much lower than is the reduction in the elimination of the dye when the early disturbance in the acid-base equilibrium of the blood occurs.

An investigation [25] concerning the way in which uranium induces the kidney injury appeared some years ago. In this study it was shown that the toxic effect of uranium for the tubular epithelium of the kidney could be prevented by the use of intravenous injections of sodium carbonate prior to the use of uranium. If the disturbance in the acid-base equilibrium of the blood was prevented by the use of such an alkaline solution, uranium lost its selective and toxic effect for the renal epithelium. It was furthermore shown that such an alkaline solution had no detoxicating effect on a solution of uranium, for the uranium could be dissolved in an alkaline solution, injected subcutaneously in the usual dose and produce the acute tubular nephropathy. The way in which uranium induces a depletion of the alkali reserve

25. MacNider, William deB.: The Inhibition of the Toxicity of Uranium Nitrate by Sodium Carbonate; and the Protection of the Kidney Acutely Nephropathic from Uranium from the Toxic Action of an Anesthetic by Sodium Carbonate, J. Exper. Med. **23**:171, 1916.

of the blood which in turn is associated with the development of an injury to the tubular epithelium is now under investigation. Very recently [26] the observation has been made that in intoxications by both uranium and mercuric chlorid which induce a kidney injury that is associated with a depletion in the alkali reserve of the blood, the liver shows evidence of injury prior to the development of the kidney injury. The injury to the liver is associated with the earliest disturbance in the acid-base equilibrium of the blood. When we consider the importance of the liver in connection with oxidations, the above observation may be of importance in explaining the disturbance in the acid-base equilibrium of the blood which in turn is associated with the development of the epithelial degeneration in the kidney.

In these acutely nephropathic animals with primarily a tubular injury the elimination of phenolsulphonephthalein is rapidly reduced, and after the functional capacity of the kidney as is indicated by the output of this dye has been seriously disturbed, there occurs a retention, first of urea which is followed within twenty-four to forty-eight hours by a retention of creatinin. From this observation we infer that the phenolsulponephthalein test is a more sensitive index of renal function than are the retention tests of blood urea and creatinin. The further inference appears allowable, that all of these substances, phenolsulphonephthalein, urea and creatinin, are eliminated by the renal epithelium. This conclusion is furthermore strengthened by the study of the elimination of these substances in animals that have recovered from an acute tubular nephropathy (Group II), and by the group of naturally nephropathic animals (Group III) which have been rendered acutely nephropathic. In the animals that recover from uranium the process of recovery is characterized anatomically by a regeneration of tubular epithelium and by obliterative and sclerotic changes in the glomeruli. Associated with these anatomic findings the functional recovery of the kidney is shown first by the reappearance and an increase in the elimination of phenolsulphonephthalein, and later, when further regeneration of renal epithelium has occurred; but when more extensive destructive changes have taken place in the glomeruli, there occurs a decrease in the retention of both urea and creatinin.

The group of naturally nephropathic animals which were rendered acutely nephropathic by uranium or mercuric chlorid has shown a similar type of functional response. These animals had a definite chronic glomerulonephropathy which was out of proportion to the degree of tubular injury. In such animals there was a moderate reduction in the elimination of phenolsulphonephthalein and blood urea and

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26. MacNider, William deB.: On the Occurrence of Degenerative **Changes** in the Liver in Animals Intoxicated by Mercuric Chlorid and Uranium **Nitrate,** Proc. Soc. Exper. Biol. & Med. **16**:82, 1919.

creatinin were either normal or showed a slight retention. When, however, an acute tubular injury was superimposed on the chronic vascular pathology by the use of uranium or mercuric chlorid, there occurred a sharp reduction in the elimination of phenolsulphonephthalein which in eight animals became negative within twenty-four hours, and also a rapid retention of both urea and creatinin.

A study of the disturbance in the acid-base equilibrium of the blood in the later stages of the acute nephropathy from uranium, shows that as the severity of the tubular injury increases, there is a progressive decrease in the alkali reserve of the blood and an associated reduction in the tension of carbon dioxid in alveolar air. This disturbance may go to the point of placing the animal in a state of air hunger and coma. During this depletion in the alkali reserve of the blood, there appears in the urine both acetone and diacetic acid. After a certain degree of functional disturbance has been produced in the kidney, the elimination of these ketone bodies is decreased and associated with this change in their quantitative output, there occurs a further reduction in the alkali reserve of the blood. From this observation it is inferred that a part of the depletion of the alkali reserve of the blood which occurs late in a tubular injury of the kidney is due to a retention of acid bodies which is dependent upon the inability of the severely damaged tubular epithelium to eliminate such substances. This inference is strengthened by the further observation that when animals recover from the acute tubular injury by the regeneration of tubular epithelium, as is shown by an increase in the elimination of phenolsulphonephthalein and by a decrease in the retention of urea and creatinin, there occurs an increase in the output in the urine of both acetone and diacetic acid. Associated with the increased elimination of these bodies, there occurs an increase in the alkali reserve of the blood and an increase in the tension of alveolar air carbon dioxid.

With the improvement in renal function of animals recovering from an acute uranium nephropathy there is a continued increase in the alkali reserve of the blood which may reach the point of normality. In such animals, even though sufficient regeneration of tubular epithelium has occurred to maintain a normal acid-base equilibrium, the existence of the chronic nephropathy is indicated by the low output of phenolsulphonephthalein and by the retention of urea and creatinin. A similar observation has been made for the naturally nephropathic animals. Such animals with a marked glomerulonephropathy and relatively well preserved tubular epithelium may show a normal alkali reserve of the blood and yet the elimination of phenolsulphonephthalein may be low and there may or may not be a retention of urea and creatinin. The existence of a normal alkali reserve of the blood is,

however, no index of the stability of the acid-base equilibrium. When such animals are given either uranium or mercuric chlorid, there occurs a very rapid depletion of the alkali reserve with an associated injury to the tubular epithelium, a very rapid reduction in the elimination of phenolsulphonephthalein, a retention of blood urea and creatinin and a decrease in urine formation which soon leads to the establishment of an anuria.

CONCLUSIONS

1. The acute tubular nephropathy which is produced by uranium is associated with the ability of the metal to effect a disturbance in the acid-base equilibrium of the blood. The tubular injury is more marked in an old animal than in a young animal. In an old animal the depletion of the alkali reserve of the blood occurs more rapidly and is more pronounced than is the case in a young animal.

2. This injury to the kidney is indicated functionally, first by a reduction in the elimination of phenolsulphonephthalein and later by a retention of blood urea and creatinin.

3. Asssociated with the establishment of such an injury both albumin and casts appear in the urine. The amount of albumin in the urine is no index of the severity of the pathology in the kidney or the degree of functional disturbance. The quantitative output of albumin may show a progressive decrease, while at the same time the elimination of phenolsulphonephthalein is rapidly decreasing, and both urea and creatinin are showing a retention.

4. A certain number of the animals rendered acutely nephropathic by uranium have recovered from the acute injury with the development of a chronic nephropathy. Those animals which effected a recovery were young animals. The old animals were unable to establish and further those changes of repair which lead to recovery with a chronic nephropathy. The changes in the kidney during the period of recovery have consisted in the regeneration of tubular epithelium of a flattened and less specialized type and of the production of chronic obliterative and sclerotic changes in the glomeruli. With the establishment of this type of chronic injury there occurs an increase in the alkali reserve of the blood which may reach the point of normality. There is an increase in the elimination of phenolsulphonephthalein and a decrease in the retention of blood urea and creatinin.

5. From these anatomic and functional observations the inference is drawn that the tubular epithelium is of more importance in maintaining a normal acid-base equilibrium of the blood, and is more concerned with the elimination of phenolsulphonephthalein, urea and creatinin than is the vascular mechanism of the kidney.

6. Similar observations have been made in a group of naturally nephropathic animals in which the chronic injury to the kidney has consisted in a glomerulonephropathy with histologically well preserved tubular epithelium. In such animals the reserve alkali of the blood may be normal, the elimination of phenolsulphonephthalein may be only slightly reduced, and there may be no retention of blood urea and creatinin. When, however, an acute tubular injury is superimposed on this chronic injury by uranium or mercuric chlorid there occurs an early edema and necrosis of the tubular epithelium without the development of any acute injury to the glomeruli. Such an injury has been associated with a rapid depletion of the alkali reserve of the blood and an associated decrease in the tension of carbon dioxid in alveolar air. The acute injury is expressed functionally by a rapid reduction in the elimination of phenolsulphonephthalein and by a retention of blood urea and creatinin. The animals become acutely anuric and die in convulsions or in a coma which may not be preceded by convulsions.

7. The present investigation, which has been concerned with certain functional and anatomical studies in different types of nephropathic processes, tends to minimize the importance of the glomerulus as a functional unit and to emphasize the relative importance of the tubular epithelium. The investigation furthermore points out the influence of a disturbance in the acid-base equilibrium of the blood on the histology and functional capacity of the renal epithelium.

HIGH PROTEIN DIETS AND ARTERIOSCLEROSIS IN RABBITS

A PRELIMINARY REPORT *

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In studies dealing with the effect of high protein diets on the kidneys of rabbits,[1] it was noted that the animals which ate such diets for a number of months, showed at necropsy widespread arteriosclerosis of the aorta. It was further noted that the extent of the vascular disease was roughly proportional to the duration of the high protein diet.

Thus, the notes from a group of rabbits fed a mixture whose protein content was made high by means of casein[2] gives the following information in regard to the condition of the aorta:

Rabbit 56: Weight, 2,950 gm.; casein diet three weeks. Aorta normal.

Rabbit 54: Weight, 2,270 gm.; casein diet, two and one-half months. Aorta normal.

Rabbit 61: Weight, 2,500 gm.; casein diet, eleven months. The arch and thoracic portion of the aorta show many raised plaques and streaks.

Rabbit 57: Weight, 1,815 gm.; casein diet one year. The root, the ascending limb of the arch and to a lesser extent the thoracic aorta, show many irregular raised yellow plaques and streaks.

Rabbit 58: Weight, 2,725 gm.; casein diet one year. The root, the ascending limb and the arch of the aorta show many discrete and confluent raised yellow patches and streaks.

In another group of rabbits fed a diet consisting of a mixture of dried powdered beef and bread flour in the proportion of one to two, the notes dealing with the condition of the aorta read as follows:

Rabbit A-1: Weight, 2,522 gm.; meat diet four weeks. Two very small raised yellow patches in the thoracic aorta.

Rabbit B-1: Weight, 2,000 gm.; meat diet six weeks. Aorta shows one small patch of arteriosclerosis about 2 mm. in diameter.

Rabbit A-2: Weight, 1,240 gm.; meat diet three months. Beneath each cusp of the aortic valves is a raised pale yellow plaque. The orifices of some of the vessels leaving the aorta are surrounded by raised irregular yellow rings. A number of raised patches are seen in the arch of the aorta.

Rabbit B-2: Weight, 2,090 gm.; meat diet four and one-half months. Small raised patches occur at the opening of every vertebral artery and at the openings of the subclavians. A number of raised yellow patches are seen in the arch of the aorta.

Rabbit A-4: Weight, 2,380 gm.; meat diet seven months. The thoracic aorta shows very many pale yellow raised streaks and plaques. These areas are so numerous in the arch that they form a continuous layer.

Rabbit B-3: Weight, 2,870 gm.; meat diet seven months. The thoracic aorta from the bases of the valves to the diaphragm shows many large raised pale yellow patches. A few similar patches are seen in the abdominal aorta.

The two obvious sources of error in assuming that the vascular lesion observed bears a causal relationship to the diet are: first, that arteriosclerosis may be a lesion of very frequent occurrence in laboratory rabbits; and second, that arteriosclerosis may be common in old rabbits, and that the experimental rabbits in which the arteriosclerosis was found were old and would, therefore, be expected to show a high incidence of this vascular disease.

The frequency of spontaneous arteriosclerosis in laboratory rabbits has been investigated by several authors. Hedinger and Loeb[3] state that "spontaneous arterial disease has not been observed in rabbits so far as has been shown by the literature. We ourselves have never found such lesions in about one hundred rabbits that were investigated with that in view." Miles,[4] on the other hand, found aortic lesions in seventeen of forty-nine (34.6 per cent.) supposedly normal rabbits. She adds that rabbits obtained from a dealer raising them for the market in large numbers and in close quarters showed a higher percentage of lesions than those obtained from other sources. Bailey[5] studied the effect of diphtheria toxin on the arteries of rabbits. Thirty-five animals were used. Three of these were controls and showed normal vessels. The thirty-two others were treated with the intention of producing vascular lesions. Of these the vessels were normal in twenty-seven. Hence, in 84 per cent. of rabbits treated by Bailey with the intention of producing arteriosclerosis, no vascular lesions were found.

The experience of other workers who have investigated the frequency of arteriosclerosis in supposedly normal rabbits may be summarized by the statement that vascular lesions may be expected in occasional rabbits assumed to be normal, but that spontaneous arteriosclerosis is not an important source of error when the majority of a group of rabbits shows vascular lesions.

In order to control our observations still further, we have examined the aortas of fifty-nine rabbits, twenty of which had been used in the

3. Hedinger and Loeb: Arch. f. exper Pathol. **56**:314.
4. Miles: Spontaneous Arterial Degeneration in Rabbits, J. A. M. A. **49**: 1173, 1907.
5. Bailey: J. Exper. M. **25**:109, 1917.

laboratory course in pharmacology and the remainder of which had been used in the laboratory of internal medicine. The aortas of all these rabbits, with two exceptions, were normal. The first exception was formed by a rabbit whose aorta presented a single raised patch, 1 mm. in diameter. This animal had been in the laboratory seven and one half months. It had had "snuffles" during all these months, had been immunized against the typhoid bacillus seven months previously, and at necropsy was found to have pneumonia. The second abnormal aorta showed a small, slightly raised, sclerotic patch near an aortic cusp, and several very small raised yellow patches in the arch. The outcome of the investigation of this large number of control animals fully justifies the statement that arteriosclerosis of the aorta is a very uncommon lesion in untreated rabbits.

The second possible source of error, namely, that arteriosclerosis may be common in senile rabbits, will not account for the vascular lesions found in the group of animals which ate the meat mixture, since these rabbits were not senile. Their high protein diet was begun when they were about 6 months old. Consequently, the oldest of them could not have been more than 13 or 14 months old when killed.

The proportionality existing between the length of the high protein feeding and the amount of vascular injury, serves to emphasize the view that the high protein diet was either directly or indirectly the cause of the arteriosclerosis.

A description [6] of the microscopic appearance of the lesion kindly furnished me by Dr. C. V. Weller reads as follows: "Rabbit 58.— Aorta. Hemalum and eosin and Van Gieson's stains. The intima is thickened irregularly through the presence of elevated plaques, many of which are three or four times as thick as the normal aortic wall. These elevated patches in most cases involve only the intima. In a few instances, the innermost lamellae of the media are included. The elevated patches show a proliferation of the intima, increase in the elastic fibers and large areas of secondary fatty degeneration and lique-faction necrosis, accompanied by marked formation of cholesterin. The picture is that of an advanced intimal atherosclerosis in varying stages up to and including secondary atheromatous change with choles-terin formation. The greater part of the media and adventitia are negative."

It is evident from this description that we are dealing with true arteriosclerosis as it occurs in the human being.

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6. This description was published as part of a footnote in the paper entitled "The Production of Bright's Disease by Feeding High Protein Diets, loc. cit.

THE ALKALI RESERVE IN PELLAGRA

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In the urinary findings of thirty-one cases of pellagra studied at the U. S. Pellagra Hospital, Spartanburg, S. C., in the spring and summer of 1917, fourteen patients showed high ammonia and low urea ratios. Of the fourteen high ammonia ratios, the ammonia was relatively increased in eight, while in the remaining six the urinary output of ammonia was much increased over that of four normal persons serving as controls. In some cases the ammonia nitrogen ran as high as 20 per cent. of the total nitrogen. In a number of cases subsequent to 1917, a high ammonia ratio was found at the time the patient entered the hospital.[1]

Though it was well recognized that a high ammonia ratio, whether the ammonia is relatively or absolutely increased, is susceptible of other explanations than a depletion of the normal alkali reserve of the body, or a state of acidosis, the urinary findings spoken of suggested that in some cases, at least, there might be a greater or less depletion of the alkali reserve.

In regard to acidosis in pellagra, Fairbanks[2] believes that pellagra is caused by an acidosis resulting principally from phosphoric acid and purins in the blood. Carmichael,[3] on the contrary, considers that the disease is due to an increase in the alkalinity of the blood caused by the excessive ingestion of fruits and vegetables. Jobling and Maxwell,[4] using the Van Slyke method (they do not state how the blood was collected) found the average carbon dioxid volume per cent. to be 61.63 in twenty acute cases and 57.27 in sixteen chronic cases, and concluded that the alkali reserve of the blood in pellagra does not vary from normal in either the acute or the chronic cases and that, therefore, there is no acidosis or alkalosis in pellagra. Very recently there came to our notice a British report on pellagra[5] wherein is reported some evidence of acid intoxication in pellagra as deduced from the facts that there was found a slight increase in the ammonia and in titratable acid of the urine in twenty early cases of pellagra, using phenol-

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1. The results of the urine work will be published later.
2. Texas State M. J. **21**:170, 1916.
3. Quoted by Jobling and Maxwell: J. A. M. A. **69**:2026 (Dec. 15) 1917.
4. Loc. cit.
5. Report of a Committee of Inquiry Regarding the Prevalence of Pellagra Among the Turkish Prisoners of War, p. 36, Sec. B, 1918.

phthalein as indicator, and in tests in eight early cases of pellagra and four well marked cases a slight decrease in the fixed alkali of the blood as determined by titrating with dimethyl-amino-azobenzene as indicator.

The study of the alkali reserve here was started late in the summer of 1917, subsequent to the findings of a tendency to a heightened ammonia ratio and subsequent to the crest of the pellagrous wave for that season.   During these last two seasons pellagra was far less abounding and the cases in the hospital were far less severe than in previous years.

In the study herein described two methods of procedure were employed: First, the determination of the venous carbon dioxid tension by the Plesch [6] method as modified by Higgins [7] and described in detail by Marriott; [8] and second, the carbon dioxid bound by the blood plasma by the Van Slyke and Cullen [9] method using the Van Slyke [10] carbon dioxid apparatus.

For the sake of brevity and quick elucidation of the alveolar air method, we may quote Van Slyke and Cullen [11] who cover the subject so well.

"1. Arterial carbon dioxid tension (Haldane method).   The alveolar air as shown by A. and M. Krogh is in equilibrium in respect to its carbon dioxid content with the arterial blood.   Consequently, in accordance with the law of gas solubility the concentration of carbon dioxid in the alveolar air is directly proportional to that of free carbonic acid in the blood.   Consequently, the carbon dioxid concentration of the alveolar air is through the intermediary parallelism of the blood carbonic acid, kept proportional to arterial sodium bicarbonate   All three concentrations go up and down together, the blood bicarbonate fixing level of the carbonic acid, and the latter that of the alveolar carbon dioxid.   Under pathologic conditions, or under the influence of drugs, of decreased atmospheric oxygen tension, or of anxiety or excitement, the sensitiveness of the respiratory control may vary so that the alveolar carbon dioxid is not under all conditions even an approximate measure of the bicarbonate reserve.   All sources of error together, however, even in pathologic conditions, are in most cases encountered within such limits that the clinical utility of carbon dioxid determinations as measure of the alkali reserve of the blood is thoroughly established, although the fact that so many factors beside the alkaline reserve of the blood can affect the alveolar carbon dioxid tension certainly make the latter far from an ideal measure of the former.

"2. Venous carbon dioxid (Plesch method).   The Plesch method differs from the Haldane in that the air analyzed, instead of being taken at the end of a single quick expiration, is breathed in and out of a rubber bag by the subject for from thirty to forty seconds.   Consequently, the carbon dioxid tension approaches more nearly that of the venous than of the arterial blood, the Plesch results being, as a rule, from 4 to 6 mm. higher in carbon dioxid ten-

6. Ztschr. Exper. Pathol. u. Therap. **6**:380, 1909.

7. Carnegie Institute of Washington, Publ. 203, p. 168, 1915.

8. J. A. M. A. **66**:1594 (May 20) 1916.

9. J. Biol. Chem. **30**:289, 1917.

10. Ibidem, 347.

11. Loc. cit., pages 299, 300.   See this article for references to alveolar air determination under normal and pathological conditions.

sion than the Haldane results. Since the venous carbon dioxid tension runs fairly parallel with the arterial, however, the Plesch results may be taken as indirect measures of the arterial bicarbonate and, so to say, one degree less direct than the Haldane. An advantage of the Plesch technic is that it requires less cooperation on the part of the subject than the Haldane procedure."

The Plesch method was used by us. In the details on the method of collecting the samples of air and the technic of the method of analysis, etc., the directions given by Marriott [8] were followed closely. This method determines the venous carbon dioxid tension, that is, the concentration of carbon dioxid in the alveolar air in equilibrium with the carbon dioxid content of the venous blood. In acidosis the concentration of the carbon dioxid of the alveolar air is diminished.

In normal adults at rest, the carbon dioxid tension in the alveolar air, determined by the Plesch method, varies from 40 to 45 mm. Tensions between 30 and 35 mm. are indicative of a mild degree of acidosis. When the tension is as low as 20 mm. the individual may be considered to be in imminent danger. We regard values of 35 mm. and over as normal. The Plesch method, as pointed out by Van Slyke and Cullen, may be taken as an indirect measure of the alkali reserve. The Van Slyke method of determining the carbon dioxid bound by the blood plasma is a direct determination of the alkali reserve of the body, that is, the excess of base which is left after all the nonvolatile acids have been neutralized and is available for the immediate neutralization of further acids.

ALVEOLAR AIR METHOD

The venous carbon dioxid tension was determined (1) on patients who had been in the hospital some time and had shown marked improvement; (2) on patients who had been in the hospital a longer or shorter time but with a slower change for the better, and (3) on patients recently admitted and still in a marked stage of pellagra. The condition of the patients from a pellagra standpoint, irrespective of their condition at the time of entering the hospital (which condition, of course, was noticeably pellagrous for them to obtain admission), was noted at the time the tests were made. The only treatment, barring marked complication, was nutritional. The diet of the patients varied. At the time of testing some had been on a very generous hospital diet with meat, milk, eggs, fruits, etc.; others had been on a similar hospital diet, but with less milk, meat, etc., while still others, who were tested on or very shortly after admission, had been on a rather slim diet, as far as could be ascertained, with little meat, milk or eggs. As the diet seemed to play little part in the degree of acidosis, the diet records, where known, are not herein listed.

TABLE 1.—Venous Carbon Dioxid Tension in Pellagra

Case No.	Sex	Age	Carbon Dioxid Tension	At-tack	Ammonia Nitrogen, Total Nitrogen, Per Cent.	Status of Pellagra at Time of Testing
1918						
325	M.	48	40.0	1	4.99	Cured
337	M.	46	37.5	1	7.00	Cured
341	F.	18	40.0	1	5.14	Cured
353	F.	36	35.0	6	8.22	Considerable improvement; now a moderate case
357	F.	35	42.5	1	4.73	Much improved. Now a mild case
358	F.	26	37.5	1	6.66	Practically well. Skin lesions practically cured. Now a mild case
369	M.	37	37.5	1	4.86	Improving; still some skin lesions; now a moderate case
370	M.	57	35.0	2	8.72	Markedly pellagrous
371	F.	65	37.5	2	4.91	Moderately pellagrous
372	M.	44	35.0	2	3.38	Very markedly pellagrous
375	M.	47	42.5	4	6.92	Very markedly pellagrous
376	M.	34	32.5	2	2.07	Weak and moderately pellagrous; residual skin lesions
378	F.	29	40.0	3	10.32	Moderately pellagrous; slight skin lesions
1919						
539	M.	65	32.5	1	3.2	Convalescing slowly; considerable skin lesions; now a moderate case
557	M.	60	35.0	2	....	Practically cured
563	M.	45	32.5	1	....	Practically cured. Given cascara several hours previous to test
570	F.	23	32.5	5	....	Practically cured. Nursing an infant
571	M.	59	25.0	2	4.3	Pellagra cured. Asthmatic
572	F.	14	32.5	1	....	Practically cured
573	M.	50	32.5	7	....	Practically cured
574	M.	60	35.0	1	5.5	Cured
576	F.	43	35.0	2	4.0	Almost well; now a very mild case
581	F.	29	32.5	2	10.8	Almost well; now a very mild case
583	F.	27	32.5	2	3.6	Cured. Nursing an infant
585	F.	39	32.5	6	4.2	Improving rapidly; now a mild case
586	F.	56	32.5	2	10.0	Improving, desquamating; now a mild case
587	M.	47	27.5	2	3.0	Markedly pellagrous, complicated with edema
1919*						
1	M.	54	32.5	2	3.7	Mild case
3	F.	50	32.5	1	8.7	Marked case
5	M.	30	32.5	1	4.9	Mild case. Asthmatic
7	M.	68	42.5	1	3.2	Very mild case
10	F.	24	35.0	1	8.8	Moderate case, desquamating. Occasionally nurses 14 months old infant
11	F.	36	32.5	2	3.3	Mild case. Nursing an infant
12	F.	48	32.5	1	6.0	Moderate case, desquamating
13	M.	44	40.0	..	4.7	Sent in as pellagrous. Diagnosis not confirmed
15	F.	39	42.5	4	3.1	Mild case, desquamating. Nursing an infant
16	M.	28	30.0	1	4.0	Marked case, desquamating
17	F.	18	25.0	1	5.8	Severe; complicated with thyroprivia
19	M.	58	42.5	2	3.2	Moderate case, desquamating
20	F.	28	42.5	2	15.8	Mild case, desquamating
21	F.	15	37.5	4	4.6	Moderate case, slight erythema
22	F.	38	40.0	9	3.0	Mild case, desquamating
23	F.	21	37.5	1	6.6	Mild case, desquamting
24	F.	41	37.5	3	2.12	Mild case, desquamating
25	F.	20	32.5	1	12.8	Mild case

* A new series of case numbers was started July 1, 1919.

The average venous carbon dioxid tension of the forty-four pellagra patients tested by the alveolar air method was 35.23 mm. Leaving out four complicated cases, two patients with asthma, one patient with beriberi symptoms, and one patient with thyroprivia, complications which might affect the alveolar air determinations, the average of the forty uncomplicated cases was 36.00 mm. Of these forty patients, twenty-four, or 60 per cent., had a venous carbon dioxid tension of 35 mm. or over with an average of 38.44 mm. In sixteen cases,

or 40 per cent., the carbon dioxid lay between 30 and 35 mm., suggestive of a mild degree of acidosis. Five of these sixteen patients, however, when further tested by the Van Slyke method for carbon dioxid bound by the blood plasma gave carbon dioxid values of practically 60 volume per cent. and over, so there was no lack of alkali reserve. Ten of the forty patients tested by the alveolar air method were cured of pellagra at the time the test was made, that is, the erythema and roughness of the skin had disappeared, the patients had gained in weight and had a general feeling of well being and were to be discharged shortly. The average carbon dioxid tension of these ten patients was 35 mm. The average of the other thirty cases, with slight or marked pellagra, was 36.33 mm. This figure is probably slightly lower than it should be, since a few of the patients in 1919 were tested in the afternoon, when the results would undoubtedly be slightly lower than if taken in the morning. All the determinations, too, were made in the hot summer when some salt loss might be expected by reason of sweating.

TABLE 2.—VENOUS CARBON DIOXID TENSION IN PELLAGRA PATIENTS ARRANGED IN FOUR GROUPS

Very Marked Pellagra, Mm.	Moderate Pellagra, Mm.	Mild Pellagra, Mm.	Cured of Pellagra, Mm.	Average of Twenty-One Controls, Mm.
35.0	35.0	42.5	40.0	
42.5	37.5	37.5	37.5	
42.5	37.5	35.0	40.0	
32.5	32.5	32.5	35.0	
30.0	40.0	32.5	32.5	
	32.5	32.5	32.5	
	35.0	32.5	32.5	
	32.5	42.5	32.5	
	42.5	32.5	35.0	
	37.5	32.5	32.5	
		42.5		
		40.0		
		37.5		
		37.5		
		32.5		
Average 35.0	36.25	36.83	35.0	39.76
Per cent. 35 mm. or over 60.0	70.0	60.0	50.0	90.48

The relation of acidosis to pellagra, as tested by the alveolar air method, is further brought out in Table 2 in which the patients are grouped, according to their condition when the tests were made, into those with marked pellagra, those with moderate pellagra, those with mild pellagra, and those who were considered cured of pellagra.

Despite the fact that whatever error there might be in our technic would tend to make our results low, it may be seen (1) that the majority of the hospital patients tested by the alveolar method of testing acidosis was normal; (2) that in those cases where the carbon dioxid tension was somewhat subnormal, the subnormality as shown in

Table 2, had nothing to do with the severity of the pellagra symptoms as judged primarily by the extent of the erythema and dermatitis and secondarily by the state of malnutrition and general weakness, and (3) that in general the patients gave slightly lower venous carbon dioxid tension than did the controls [12] who were regarded as normal.

The twenty-one nonpellagrins as controls, normal as far as known, gave venous carbon dioxid tensions from 32.5 (two cases) to 45 mm., with an average of 39.76 mm.

CARBON DIOXID BOUND BY THE BLOOD PLASMA

The Van Slyke-Cullen method of estimating the carbon dioxid of the blood plasma was used. The blood was drawn from the arm vein directly into a centrifuge tube containing potassium oxalate (about 0.5 per cent. of the weight of the blood drawn) and paraffin oil. The blood was stirred by means of the inlet tube and centrifuged immediately, and the carbon dioxid of the plasma was determined in duplicate samples of 1 c.c. The results are given in Table 3.

As may be seen from Table 3, the carbon dioxid bound by the blood plasma of the thirty patients (exclusive of Case 13) varied from 45.3 to 69.5 volume per cent., with a general average of 60.05. This average is almost identical with that of thirty-six pellagra patients tested by Jobling and Maxwell [3] at the Davidson County Pellagra Hospital, Tenn. They found that the average carbon dioxid volume per cent. was 61.63 for twenty acute cases, and 57.27 for sixteen chronic cases, which gives a general average of 59.69 for all their patients. [13]

According to Van Slyke and Cullen, [9] with the method employed by us (venous blood drawn under oil without stagnation of blood or loss of carbon dioxid) the minimal normal figure is 60 c.c. of carbon dioxid per 100 c.c. of plasma. Of the thirty pellagra patients tested by this method at the U. S. pellagra Hospital, twenty, or 66.67 per cent., were practically 60 volume per cent. or over, and ten, or 33.33 per cent., were below 60. The average of the ten cases below 60 was 52.4 per cent. carbon dioxid, with only two cases appreciably below 50 per cent. Of the ten cases below 60 per cent. of carbon dioxid,

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12. The controls were chemists, physicians, nurses, clerks, and attendants who had been connected with the hospital for a shorter or a longer time over the period the tests on the patients were made. All the controls were active, nonpellagrous people, with a feeling of well being and in normal health, as far as known. In their general appearance, state of nutrition, and joy of living the controls were much superior to the patients.

13. We hesitate to apply the term "chronic" to our cases since, though in many cases there had been recurrences in the spring and summer, there were, in the intervening colder months, periods of apparent well being and a toning up of the general condition and lack of erythema of the skin, in short, periods when pellagra was not manifest. Hence, the recurrences are spoken of as such and such an attack.

three (142a, 401a and 332a) were practically negative as far as external manifestations of pellagra were concerned though the patients were still rather weak; three (481, 567 and 20) were mild cases; one (502) was a moderate case, while only two cases (485 and 488) were severe.

TABLE 3.—Carbon Dioxid Bound by Blood Plasma

Case	Sex	Age	Percentage of Carbon Dioxid Bound by Plasma	No. of Attacks	Ammonia Nitrogen ——— Total Nitrogen, per Cent.	Status of Pellagra at Time of Testing
142a	M.	43	45.3; b89.9	2	....	Feeling dull and out of condition at time of first test but convalescing with skin neg.
401a	M.	37	47.5; b62.2	2	....	Receiving dilute hydrochloric acid per os at first test, weak, improving, slight skin lesions, loose bowels
471	F.	25	61.5	1	....	Improving, residual skin lesions
479	F.	40	66.4	1	....	Improving, desquamating and atrophic skin
480	M.	63	59.9	2	5.51	Improving, desquamating and residual skin lesions
481	M.	49	50.4	3	....	Improving, residual skin lesions; now a mild case
332a	F.	29	57; b56.9	2	5.01	Weak and anemic, slight skin lesions
484	M.	52	67.9	1	....	Severe, skin lesions marked
485	M.	52	50.9; b59.1	1	6.57	Severe, skin lesions marked
488	F.	30	50.4; b59	1	....	Severe, skin lesions marked
496	M.	33	59.4	1	5.83	Mild case
497	M.	36	60.0	2	20.6	Skin lesions marked
500	F.	37	59.9	8	5.65	Skin lesions marked
501	M.	31	64.7	1	16.12	Skin lesions marked
502	M.	58	56.5	1	....	Skin lesions moderate
567	M.	53	53.0	1	....	Almost well, now a mild case
585	F.	39	60.0	6	4.2	Markedly pellagra, desquamating
587	M.	47	58.8	2	3.0	Marked pellagra with edema
1919						
1	M.	54	66.6	2	3.7	Mild case
3	F.	50	67.7	1	8.7	Marked case
5	M.	30	61.7	1	4.9	Mild case
7	M.	68	67.4	1	3.2	Very mild case
10	F.	24	66.8	1	8.8	Occasionally nurses '14 mos. old infant. Moderate case; desquamating
11	F.	36	59.5	2	3.3	Mild case. Nursing an infant
12	F.	48	69.5	1	6.0	Moderate case, desquamating
13	M.	44	66.0	...	....	Sent to hospital as pellagrous (diagnosis not confirmed)
15	F.	39	60.1	3	3.1	Mild case, desquamating. Nursing an infant
16	M.	28	61.0	1	4.0	Marked case
19	M.	58	68.4	2	3.2	Mild case
20	F.	28	54.6	2	15.8	Mild case
22	F.	38	68.6	9	3.7	Mild case

a. Second test of alkali reserve after another month in the hospital, with marked improvement in general condition and with the pellagra symptoms negative or practically so.

It would seem, then, that in the cases of pellagra studied the carbon dioxid bound by the blood plasma was for the most part normal, that in a minority of cases the carbon dioxid bound by the plasma was slightly subnormal, but that this subnormality was not relatable to the severity of the pellagra symptoms.

Of the seventy uncomplicated cases of pellagra tested by the two methods, venous carbon dioxid tension and carbon dioxid bound by the blood plasma, fourteen cases were duplicates by the two methods. Of the fifty-six separate cases tested for alkali reserve by the two methods, none showed a marked depletion of the alkali reserve, about one-third showed a slightly subnormal level, while the greater number of cases were within normal limits.

THE RELATION OF THE URINARY AMMONIA RATIO TO THE CARBON DIOXID TENSION AND THE CARBON DIOXID BOUND BY THE BLOOD PLASMA

In Tables 1 and 3, the urinary ammonia ratio is given for a number of cases at or near the time the tests specifically designated in the two tables were made. A number of the patients had previously a very high ammonia ratio, but only the ratio at the time of the carbon dioxid analyses were made is herein considered. The analysis of normal urines here showed that the ammonia nitrogen did not go above 7 per cent. of the total nitrogen. Accordingly, ratios of ammonia nitrogen to total nitrogen above 7 per cent. were regarded as high, 7 per cent. or below 7 per cent. as normal. Of the thirty-eight cases included in Table 1, analyzed for carbon dioxid tension and urinary ammonia and total nitrogen, only four patients showed concomitantly a high ammonia ratio and a low carbon dioxid tension; five patients had a high ammonia ratio and a normal carbon dioxid tension; twelve patients had a low ammonia ratio with a low carbon dioxid tension; while seventeen patients had a low ammonia ratio with a normal carbon dioxid tension. Similarly, in Table 3 dealing with carbon dioxid bound by the plasma, the ammonia ratio was over 7 per cent. of the total nitrogen in five cases. Only one of these five patients (Case 20) showed a low percentage of carbon dioxid bound by the plasma, namely, 54.6 per cent. The other four patients with high ammonia ratio (Cases 497, 501, 3 and 10) showed a normal percentage of carbon dioxid bound by the plasma. On the other hand, three cases (332a, 485 and 587) showed a lowered alkali reserve with a normal urinary ammonia ratio. Thirteen of the cases analyzed for both factors, or approximately 62 per cent., were normal both as to ammonia and as to the carbon dioxid bound by the plasma.

It would seem, then, from a consideration of the relation of the ammonia ratio to the carbon dioxid tension of the alveolar air and the carbon dioxid bound by the plasma, that, barring other diagnostic factors, the urinary ammonia ratio is not a measure of acidosis or lack of alkali reserve.

GENERAL CONCLUSIONS

Of the fifty-six patients tested for alkali reserve by the alveolar air method and by the determination of the carbon dioxid bound by the blood plasma, none showed a marked depletion of the alkali reserve, about one-third showed a slightly subnormal level, while the greater number were within normal limits. There would seem to be little uncompensated acidosis in pellagra.

RECOVERY FROM TUBERCULOUS MENINGITIS AFTER TREATMENT WITH INTRASPINAL INJECTIONS OF ANTIMENINGOCOCCIC SERUM *

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The treatment of tuberculous meningitis has always been more or less haphazard, largely symptomatic, and entered upon by the clinician with very little enthusiasm and with even less hope of success because of the very general opinion of the uniform fatality of the disease. It has been possible, however, to collect from the literature about forty cases of unquestionable tuberculous meningitis terminating in recovery, and we wish to report four cases of the disease which have terminated in recovery.

It will not be within the scope of this paper to review the literature of recoveries from tuberculous meningitis, as this has been most admirably done by Alfred E. Martin [1] in 1909. His critical survey of the reports on such cases up to that date show that of thirteen cases with remission, varying from four months to five years, and terminating in death, only eight were undoubted cases of tuberculous meningitis; and of the cases ending in permanent recovery, only twenty-five were definitely proven to be cases of tuberculous meningitis. Some writers, as Babinski and Strumpel, strongly maintain that in a large proportion of the reported cases of recovery the diagnosis is incorrect, being merely cases of serous meningitis, and it is proven in that article that such is the case. During recent years, the greater exactness of diagnosis of this disease, due to the increased use of the spinal puncture as a diagnostic measure combined with refinements in examination of the fluid, has resulted in a paucity of reports of cured cases.

A careful search through the medical literature from 1910 to date has resulted in finding eleven cases ending in recovery, which have been definitely proven to be tuberculous, the criteria being the clinical course, the cell count and differential of the spinal fluid, the finding of tubercle bacilli, and the demonstration of the disease in an inoculated guinea-pig; the last two being the only real proof. Those who have reported these cases are Castaigne and Gourand,[2] Barbier and

1. Martin, A. E.: Occurrence of Remissions and Recovery in Tuberculous Meningitis, Brain **32**:209, 1909.

2. Castaigne and Gouraud: J. Méd. Français, May 15, 1911.

Gougelet,[3] Elsner [4] having seen a case at Treupel's clinic; Reichmann and Rauch [5] had two cases, Pitfield,[6] Schaeffer,[7] Archangelsky,[8] Fonzo,[9] Tilli [10] and Dunn.[11] All of these cases were clinically and bacteriologically cases of tuberculous meningitis, and as all of the reporters used different methods of treatment, it was interesting to note the almost universal agreement that there was an improvement following removal of spinal fluid. There are also on record seven cases in which the diagnosis has not been confirmed by the recovery of the Koch bacillus from the spinal fluid, the diagnosis having rested either on the presence of tuberculosis elsewhere, the clinical course, or the cutaneous tuberculin reaction. Those who report these cases are I. Celeste,[12] Bernard and Debré,[13] Di Rinzi,[14] and Browning [15] four cases.

To the above we add the two undoubted and two doubtful cases reported in this paper. A summing up of these statistics shows that there are thirty-eight cases ending in recovery in which the diagnosis is certain, and fifteen in which it is doubtful. With these cases we will have to consider those cases ending in recovery which have never been contributed to the literature, but even with them it is not a very hopeful total in view of the apparent frequency of the disease.

STATISTICS

Statistical reports from two children's hospitals show a 100 per cent. mortality, the disease in children, as in extra miningeal tubercu-

3. Barbier, H., and Gougelet: Episodes Tuberculous meningitis curables chez les enfants, Bull. et mém. Soc. méd d. hôp. de Par. **31**:440, 1911.

4. Elsner: Tuberculous Meningitis in Monographic Medicine **6**:225.

5. Reichmann and Rauch: Ueber die Prognose und Therapie der Meningitis Zwei geheilte Faelle von Meningitis Tuberculosis, München. med. Wchnschr. **9**:1374, 1430 (July 1) 1913.

6. Pitfield, R. L.: Recovery from Tuberculous Meningitis, with Report of Cases, Am. J. M. Sc. **146**:73, 1913.

7. Schaeffer, S.: Tuberculous Meningitis; a Case with Recovery, New York M. J., Jan. 11, 1913.

8. Archangelsky, W. G.: Zur Frage über die Moeglichkeit einer Heilung der Tuberculosen Meningitis, Jahrb. f. Kinderh. **74**:155, 1911.

9. Fonzo, F.: Sulla Guaribilita della meningitie tubercolare, Pediatria **23**:334, 1915.

10. Tilli, P.: Autoserotherapy of Tuberculous Meningitis, Policlinico, Rome **23**: 1916.

11. Dunn, C. H.: Tuberculous Meningitis, Arch. Pediat. **27**:685, 1910.

12. Celeste, I.: Sulla curabilita della Meningitie tubercolare, Gazz. d. osp., Milano **31**:1137, 1910.

13. Bernard, L., and Debré, R.: Bull. et mém. Soc. méd. d. hôp. de Par. **30**:587, 1910.

14. Di Rinzi, E.: Di un cas de meningitie tubercolare sequito da guarigione, Boll. d. Clin., Milano **27**:367, 1910.

15. Browning, C. C.: Four Cases of Tuberculous Meningitis with Arrest, Med. Rec. **86**:325, 1914.

losis, being more virulent than in adults. Holt [16] mentions such statistics, as does A. E. Meyers [17] in a series of 105 cases, the patients being under 10 years of age. Statistics [1] collected from a large London General Hospital and from one in Vienna show nearly the same results, except for several indefinite cases ending in recovery. A careful analysis of the cases on the pediatric and medical services at St. Luke's Hospital, from 1898 to date, show a uniform fatal result, except for the few cases we report. There have been ninety-three cases in patients under 15 years of age, with no recoveries, while among patients over 15 years there were forty-five deaths and four recoveries. This makes a total of 142 cases during the past 20 years, with a mortality of 99.2 per cent. In the face of these discouraging reports, it is not surprising that writers on this disease consider recovery an impossibility. They do not seem to appreciate that there is an opportunity, however small, for remission or cure by prompt and unremitting treatment, and they are usually content to make a diagnosis and treat their hopeless patient symptomatically.

TREATMENT OF DISEASE

There have been many suggestions for therapy in this disease, but this very multiplicity reveals their inefficacy. Among these are a legion of drugs which have been found of value in other forms of tuberculosis, such as forced feeding, application of leeches to the mastoid, tuberculin and hexamethylenamin for its supposed bactericidal effect in the spinal fluid. In the prewassermann years these patients were frequently given large doses of potassium iodid (600 grains per day), and mercury by mouth or by inunction. This is still persisted in by some clinicians, but the refinements in the diagnosis of neurosyphilis enable us to differentiate between these two conditions. Operation in the form of decompression and opening into the cisterna magna has been advocated by C. W. Stiles [18] and H. E. Alexander,[19] being compared by the latter to a laparotomy for the relief of peritoneal tuberculosis, while its relief of pressure recommends it to the former.

Since the introduction of spinal puncture by Quincke, in 1891, this procedure has come to be looked on more and more as a therapeutic as well as a diagnostic aid, so that it is now largely employed for the relief, even though temporary, of all forms of increased intra-

16. Holt, L. E.: Tuberculous Meningitis, Am. J. Dis. Child. **1**:26, 1911.

17. Meyers, A. E.: Tuberculous Meningitis. A Study in Children; 105 Cases, Am. J. Dis. Child. **13**:427 (May) 1915.

18. Stiles, C. W.: Tuberculous Meningitis, Proc. Sixth Internat. Cong. Tuberc., 1908.

19. Alexander, H. E.: Tuberculous Meningitis, The Postgraduate, N. Y. **27**: 769, 1912.

cranial pressure whether from uremia, "wet brain," encephalitis, brain tumor or meningitis. In the large series of children noted above, Meyers [11] reports that those treated by repeated spinal puncture showed a longer duration of the disease, and to this therapeutic method both Riebold and Rumpel ascribe the cure of their cases. Pitfield's [6] patient showed great immediate improvement following the withdrawal of 80 c.c. of spinal fluid with subsequent complete recovery. Oppenheim, in his "System," [20] in 1910, says, "there is in my opinion no longer room for doubt as to the possibility of recovery from tuberculouus meningitis," and recommends repeated spinal punctures as the most promising method of cure. In the cases which have come under our observation, this procedure has always been followed by relief of the symptoms even though for a short time only, so it is our belief that spinal puncture, frequently repeated, should be considered a real asset in the treatment of tuberculous meningitis.

The injection of 30 c.c. of a 1 per cent. solution of iodoform in almond oil into the subdural space every six hours, has been recommended by one author, but does not seem to warrant commendation. P. Tilli,[10] basing his theory on the subcutaneous injection of chest fluid in tuberculous pleurisy, has used autoserotherapy by injecting subcutaneously from 1 to 3 c.c. of spinal fluid every three days. He reported three cases, one of which, a child, 18 months old, recovered. The rationale of this procedure does not seem very clear, and it is difficult to draw conclusions from one case. F. Raymond [21] has originated a novel procedure which was employed on French soldiers during the recent war; i. e., the injection intraspinally of sterilized air. A spinal puncture is performed, 40 c.c. of fluid are removed, and then 20 c.c. of air (previously passed through a red hot platinum needle for sterilization) is injected into the spinal canal. This is repeated on five or six consecutive days. No cures were reported. The improvement which was obtained following the treatment was possibly due to the spinal drainage accompanying it. Other Frenchmen, Bernard and Debré,[18] have recommended the intraspinal injection (after the removal of spinal fluid) of 5 mg. of sulphate of radium, repeated frequently. They report one case ending in recovery, the diagnosis of which, however, must be classed as doubtful.

One of us (A. W. H.), in 1916, was confronted with a question of diagnosis in the first case of our series, and in the interim gave many intraspinal injections of antimeningococcus serum. The very satisfactory termination of this case prompted us to follow a similar procedure in the second case, with again a favorable outcome. In addition

20. Oppenheim, H.: Textbook on Nervous Disease **11**:786.
21. Raymond, F.: Bull. et mém. Soc. méd. d. hôp. de Par. **12**:1058, 1917.

to these two cases we can report two additional cases terminating in recovery. In reviewing the literature we were interested to find a case reported by Schaefer [7] in which the same treatment was employed to good effect.

<div align="center">REPORT OF CASES</div>

CASE 1.—T. McA., male, aged 26, lawyer, was admitted to St. Luke's Hospital March 27, 1916. He had pleurisy nine years before, for the past three months he had anorexia, was drowsy at times, and complained of a general "run down" condition. Ten days before admission headache developed, gradually increasing in severity; he vomited and was drowsy, and three days before admission he vomited again with anorexia.

Physical Examination.—Patient was acutely ill; no rigidity of neck; lungs clear; bilateral Kernig sign; knee jerks sluggish; pulse large and bounding, from 60 to 70; temperature 103 F. Blood count showed slight anemia. Spinal puncture: 40 c.c. slightly turbid fluid removed under increased tension. Cells, 1,400; lymphocytes, 80 per cent.; polymorphonuclears, 20; globulin, plus; no organisms on smear or culture. Wassermann, negative. Twenty c.c. antimeningococcus serum injected. The following day the patient was very drowsy, with severe headache, stiff neck, Kernig very pronounced, knee jerks absent. Fundus examination showed no papillo-edema, no choroid tubercles. The procedure of the previous day was repeated. The third day he was irrational. Temperature, from 101 to 102 F.; pulse, 60. Spinal puncture and intraspinal serum injected. The next three days there was an improvement in symptoms. Temperature, 98.5 F.; pulse, 80. April 3, another intraspinal injection of 18 c.c of serum was given, followed by an exacerbation of all the symptoms, with rise of temperature to 102.2 F. and increased rigidity of the neck and positive Kernig. Joint pains and urticarial rash developed the following day, with vomiting—a true serum sickness, lasting four days with an immediate subsequent abatement of all symptoms of the meningeal irritation. April 20 a mild follicular tonsillitis developed, with temperature between 99 and 104 F. There was then noticed a paresis of the right side of the face and deviation of the tongue to the left, with pains in the left leg and thigh. A spinal puncture taken at that time showed globulin plus with fifty-one cells; lymphocytes, 97 per cent.; polymorphonuclears, 3 per cent. A partial paralysis of the left leg then ensued. The patient never showed difficulty in swallowing or bulbar speech as an evidence of his pontine lesion. Bright and clear mentally. May 9, he was discharged from the hospital with facial weakness entirely recovered from and only a slight weakness in the leg. One month later he was completely recovered and is now strong and well, practicing law in this city.

<div align="center">TABLE 1.—SPINAL FLUID FINDINGS IN CASE 1</div>

Date	Amount, C.c.	Pressure	Character	Cells	Lymphocytes	Polymorphonuclears	Globulin	Serum, C.c.
3/27	45	+++	Turbid	1,400	80	20	+++	20
3/28	8	+++	Turbid	.....	..	..	......	5
3/29	32	++	Sl. turbid	2,376	75	25	+++	18
4/ 3	40-50	++	Sl. turbid	346	97	3	++	20
4/22	25	+	Clear	51	97	3	+	
4/26	15	+	Clear	28	97	4	+	

At no time were tubercle bacilli found in the spinal fluid and guinea-pig inoculation revealed nothing, so this case must be classed as doubt-

ful. We have considered it as a case of tuberculous meningitis for the following reasons: History of an antecedent pleurisy; the slow onset for three months; its benign beginning, though eventually manifesting the severe clinical course of a meningitis; the development during its course of a fairly well localized crossed paralysis of the Millard-Gubler type; the presence of a moderately low cell count with persistent lymphocytosis and the failure to find any other organisms, though the most careful search was made by Dr. Fameuelener in smear and through culture.

CASE 2.—W. S. P., male, aged 26, publisher. On admission to hospital, Dec. 1, 1916, the patient also gave a history of having had pleurisy when younger. He had been losing weight for several months; presented a lack of initiative, and a general "run down" condition. Ten days previously, he began to have intermittent headaches. Three days later he came to see one of the house staff suffering from severe headache; he had no temperature and was sent home with directions to take a cathartic and acetylsalicylic acid. When admitted to hospital he had severe occipitofrontal headache, weakness, anorexia, irritability and vomiting.

TABLE 2.—SPINAL FLUID FINDINGS IN CASE 2

Date	Amount, C.c.	Pressure	Character	Cells	Lympho-cytes	Poly-morpho-nuclears	Glob-ulin	Serum, C.c.
12/2	7	++	Clear	126	100	..	++	
12/2	20	++	Clear	144	100	..	++	20
12/3	15	++	Clear	?	...	..	....	15
12/5	20	+	Clear	333	95	5	++	20
12/7	20	+	Clear	441	96	4	++	19
12/10	9	......	....	?				

Physical Examination.—Young man, acutely ill, restless, irritable, tossing about in bed; no stiffness of neck or Kernig. A tentative diagnosis of typhoid was made because of paucity of signs. The next day his temperature was 102 F.; pulse slow, bounding, of "cerebral" type. Headache continued severe, requiring morphin; nausea, vomiting and somewhat drowsy. Lungs clear, spleen not palpable; no oculomotor disturbance; neck stiff, bilateral Kernig and knee jerks more sluggish, no Babinski. Widal, blood culture and blood Wassermann all negative. Spinal puncture showed clear fluid under increased pressure; 126 cells; lymphocytes, 100 per cent.; globulin, 2 plus; tubercle bacilli found in moderate numbers (Dr. Karl Vogel). Realizing the apparent hopelessness of the case, it was determined to try the therapy which had been so successful in Case 1. That evening, 20 c.c. of meningococcus serum (Flexner) was given intraspinally, and was followed by slight relief of headache and nausea on the next day. December 4 temperature ranged between 100 and 102 F.; pulse, 60; general condition improved. The following day, a 20 c.c. intraspinal serum injection given which was repeated December 7. Both injections were followed by an exacerbation of the signs of meningeal irritation, with subsequent improvement. December 10, following a gradual decline in temperature, an urticarial rash appeared and then severe joint pain and tenderness developed. December 13, the temperature was 99 F.; serum sickness disappeared; general condition showed noticeable lack of cerebral signs with pulse assuming a normal character. December 20 temperature had been normal for a week; no stiffness of neck; Kernig absent; knee jerks more active; patient sitting up in bed; appetite good. Patient left hospital February 10, having gained 15 pounds in weight and feeling well, except for slight weakness of his legs. He served in the army in 1918 and is well today.

This case presents the typical onset and clinical course of a tuberculous meningitis, and the bacilli were found in the spinal fluid in moderate numbers. As in the previous case, a definite improvement followed the intraspinal serum injection and especially after the "serum sickness." This is an undoubted case of recovery from tuberculous meningitis.

CASE 3.—Mrs. J. T., aged 47, practical nurse; was admitted to the service of Dr. Hollis July 2, 1919, with severe headache. Her past history showed: at 18 had "typhoid pneumonia" followed by an osteomyelitis of wrist; a nephropexy at 34, and a panhysterectomy at 38; two attacks of malaria, two and four years previously. For the past two months she has had loss of appetite and weight. Ten days ago she developed an intermittent occipital headache becoming worse at night. Four days before admission she was constipated, nauseated and vomited everything taken since then.

TABLE 3.—SPINAL FLUID FINDINGS IN CASE 3

Date	Amount, C.c.	Pressure	Character	Cells	Lymphocytes	Poly-morpho-nuclears	Globulin	Serum, C.c.
7/ 2*	15	+	Sl. turbid	56	99	1	+++	
7/ 5	20	++	Sl. turbid	Bloody	...	..	.....	20
7/ 6	20	++	Bl. tinged	70	25	75	++	
7/ 7	30	++	Turbid, yellow	780	26	74	++	25
7/ 8	15	+	Turbid, yellow	1,430	20	80	++	16
7/ 9	35	+	Turbid, yellow	460	32	68	+	25
7/10*	15	++	Turbid, yellow	540	30	70	+	
7/11	20	0	Clear, yellow	621	41	59	+	20
7/15	20	0	Clear, yellow	137	59	41	+	
7/18	15	0	Clear	178	83	17	+	
7/21	15	+	Clear	81	79	21	+	
7/26	15	0	Clear	52	100	—	+	
7/31	15	+	Clear	61	98	2	+	
8/ 4	15	+	Clear	37	100	—	+	
8/ 8	18	+	Clear	27	100	—	+	
8/14	15	+	Clear	22	100	—	+	
8/19	18	+	Clear	65	100	—	+	
8/24	5	Slightly +	Clear	20	100	—	+	
8/30	10	0	Clear	15	100	—	+	
9/ 9	10	0	Clear	12	100	—	+	
9/23	12	0	Clear	26	100	—	+	
10/ 6	10	0	Clear	12	100	—	+	
11/10	7	0	Clear	10	100	—	0	

* Colloidal gold test: 7/2, 0 1 1 1.5 2 1 1 0 0 0; 7/9, 1 1 1 1 1 1 1.5 2.5 2 1.5

Physical Examination. — Well nourished; acutely ill; slight strabismus; reflexes hyperactive; some rigidity of neck and suggestion of beginning Kernig sign; temperature from 100 to 103 F.; pulse, 60. Blood count, urine and Wassermann test were negative. Spinal puncture revealed 15 c.c. fluid under increased pressure, 56 cells; 99 per cent. lymphocytes; globulin, 3 plus; spinal fluid Wassermann negative. The course of the disease from then on was very chronic. The headache and vomiting were the outstanding features of the clinical picture. Intraspinal injection of meningococcic serum was given on five occasions, and repeated spinal punctures were done after that for the relief of the distressing headache. The spinal fluid removed eight days after admission was slightly turbid, yellow, and under pressure; cell count, 540; polymorphonuclears, 70 per cent.; lymphocytes, 30 per cent.; globulin, plus and the colloidal gold chlorid curve of the meningitic type 1 1 1 1 1 1 1.5 2.5 2 1.5. Tubercle bacilli were found in this fluid. At this time the patient was suffering from severe headache and vomiting; was restless; no lethargy. There were no oculomotor disturbances. Stiff neck and Kernig were well marked. The

fundi examined by Dr. A. Wiener showed a blurring of both disks on their nasal margin and a patch of old choroiditis in the left eye; no tubercles. From this time on the temperature gradually approached the normal and symptoms abated until on discharge from the hospital, the spinal fluid showed 12 cells; 100 per cent. lymphocytes with faintly plus globulin. Inoculation of the guinea-pig showed tubercles in the spleen. After leaving the hospital she developed an anxiety state which took a persecutory trend. This cleared up in two weeks and the spinal fluid removed at that time was clear; 10 cells and negative globulin.

The clinical course and laboratory findings in this case leave no doubt in our minds as to the presence of a tuberculous meningitis. The marked cellular response in the spinal fluid, including poly-nucleosis following the injection of serum, and the rapid fall in cells soon after completion of five intraspinal injections had been given, are noteworthy.

CASE 4.—A. T., aged 28, male, builder. One of us (A. W. H.) saw the patient for several days prior to admission to St. Luke's Hospital, Sept. 18, 1919. History shows frequent tonsillitis; lumbago in 1907; gonorrhea in 1918; syphilis denied. He was discharged from the army April 2, 1919, as a captain after having been in France nine months and having participated in three major engagements. For several months he has been feeling "run down." Two weeks ago awoke with a throbbing occipital headache; three days later he vomited and there was a persistence of the headache, becoming gradually more severe. He was in bed one week before admission to the hospital, complaining of anorexia, restlessness and headache. There was no lethargy and no previous acute infection.

TABLE 4.—SPINAL FLUID FINDINGS IN CASE 4

Date	Amount, C.c.	Pressure	Character	Cells	Lympho-cytes	Poly-morpho-nuclears	Glob-ulin	Serum, C.c.
9/28/19	20	++	Clear, yellow	317	91	9	++	
9/30	20	++	Slightly tur-bid; yellow	128	86	14	++	20
10/ 2 2d Admis-sion	20	++	Clear	122	97	3	+	20
11/2	20	+	Clear	316	83	17	+	20
11/5	20	+	Clear	206	88	12	+	10
12/6	15	0	Clear	26	100	..	+	

Physical Examination.—Acutely ill; lungs clear; spleen not palpable; rigidity of neck; reflexes exaggerated; no oculomotor palsies; Kernig sign bilateral; temperature 100 F.; pulse, 60. Spinal punctures made September 19 and 21 both bloody. Blood Wassermann, negative; spinal fluid Wassermann, negative. Blood count, normal. Urine showed marked acetone and diacetic acid. September 28 a spinal puncture revealed 20 c.c. clear yellow fluid under increased pressure. Cells 317: polymorphonuclears, 9; lymphocytes, 91; globulin, 2 plus. Colloidal gold test, 05111521550000. Ophthalmoscopic examination by Dr. Coleman Cutler revealed a low grade papillo-edema, 1/2 D. Left side more marked than the right. October 12 this had almost cleared up. Two intraspinal injections of antimeningococcic serum were given with real clinical and laboratory improvement. The patient was discharged October 25 free from symptoms and signs.

Two days after discharge, after an exposure, he became nauseated and vomited. Complained of a return of headache and of severe joint pains. Could not take food. Temperature, 100 F.; pulse, from 70 to 80. Stiffness of neck had returned and bilateral Kernig. November 2, spinal fluid clear under pressure. Cells 316: polymorphonuclears, 17; lymphocytes, 83; globulin, 2 plus. Two intraspinal injections of serum were given at three day intervals with an immediate drop in cell count and disappearance of the symptoms. The patient is now well (Feb. 20, 1920).

This case presents some interesting features. The clinical course and the spinal fluid are quite characteristic of tuberculous meningitis — the long, slow onset, the mild manifestations and the low cell count with a lymphocytosis; however, as tubercle bacilli were never found in the spinal fluid or as it failed to produce lesions in the guinea-pig, the diagnosis must rest between an influenzal meningitis, a tubercular meningitis or possibly an epidemic encephalitis, though lacking most of the diagnostic features of the latter disease. The tendency to remission occurring so soon after apparent recovery should be taken as either a true exacerbation of the disease or else in view of the presence of severe joint pains it might be considered an abortive serum sickness lighting up as it did in the other cases the meningeal inflammatory signs. This case, in the absence of finding the tubercle bacilli, must be classed as a doubtful case of tuberculous meningitis.

DISCUSSION

In the above reports of cases there are two, Cases 2 and 3, which are recoveries from unquestionable tuberculous meningitis; the two remaining cases, because of the failure of positive laboratory findings, must be classed as doubtful. Against these must be balanced three cases in which the serum was used during the past four years at St. Luke's Hospital with ultimate death. To this total can be added the recovered case of Schaeffer,[7] in which spinal fluid inoculation was positive, making eight patients in all treated with antimeningococcic serum, five of whom recovered.

It is not our purpose to urge a specific treatment, as the optimum is still far from obtained, but as a method of approach, the intraspinal injection of meningococcic serum, combined with frequent spinal drainage, is a therapy by which the patient seems to have at least a chance. Three of our patients were young men in the middle twenties; two of them had had previous tuberculous lesions from which they recovered, while the other had been through a severe army campaign in France. Their physical condition was splendid, and having a localized meningeal form of tuberculosis were very favorable cases for treatment. However, the course of the disease was far from easy in any of them, and more than one consultant gave discouraging prognoses. The woman was a poor risk from the start, and her recovery seemed largely

dependent on her treatment. Of the patients receiving this method of treatment who died, two were men over 45, in whom the resistance was low, one alcoholic and one arteriosclerotic, and the other was of noticeably poor physique. They were given nine and seven intraspinal injections, respectively, with a resultant reduction in the cell count, symptoms and a prolongation of the course of the disease. The third patient, a young man, aged 27, showed no response after five injections, and rapidly succumbed to his disease.

The theoretical aspect of the therapy seems fairly well founded if we consider the very satisfactory results which have been obtained with autoserum in the treatment of the other chronic meningeal disease, syphilis of the spinal cord. Many who have used the Ogilvie or Swift-Ellis technic are quite satisfied that the benefit obtained therefrom is not from the arsphenamin, but from the irritating effect of the serum introduced. A recent report by Mehrtens and MacArthur [22] on the treatment of neurosyphilis showed that the injection of the patient's own serum resulted in a meningeal irritation, with increase in the cells as high as 2,300. We, therefore, consider that the intraspinal injection of antimeningococcic serum has two distinct actions; first, by adding to the spinal fluid certain antibodies which it is unable to develop itself and, second, by the introduction within the dura of a foreign protein in the form of horse serum. The irritative effect of the latter on the meninges produces a cellular response and a hyperemia about the site of any localized tubercle with beneficial result. It is with this theoretical background and the therapeutic results reported that we urge further investigation along this or similar lines. It has been suggested to us that the patient's own serum be given instead of the antimeningococcic serum; however, the tuberculous antibodies would at best be feeble if they had succumbed to a meningeal disease and one's own blood serum is not in a strict sense a foreign protein.

SUMMARY

1. There are reported in the literature thirty-eight undoubted cases of cured tuberculous meningitis, and fifteen in which the diagnosis is doubtful.

2. Except for these cases, the treatment as shown by hospital statistics has been 100 per cent. ineffectual.

3. Therapy has always been experimental in type in hopes of finding a cure.

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22. Mehrtens, H. G., and MacArthur, C. G.: Therapy of Neurosyphilis, etc., Arch. Neurol. & Psychiat. **2**:369 (Oct.) 1919.

4. The authors have employed intraspinal injections of antimeningococcic serum, combined with frequent spinal drainage, and report two cases of tuberculous meningitis and two others possibly tuberculous meningitis showing recovery under this method.

5. Theories as to the results are discussed.

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LETHARGIC ENCEPHALITIS: SYMPTOMATOLOGY AND HISTOPATHOLOGY *

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Our present literature is teeming with symptomatology and case reports of lethargic encephalitis. Since v. Economo,[1] in the spring of 1917, reported his first thirteen cases in detail, similar clinical conditions have been observed on the Eastern Continent as well as in this country. It first manifested itself on our Eastern coast in the fall of 1918 (Abrahamson [2]), gradually spreading westward. In the spring and summer of 1919, cases were reported throughout the Middle West (Bassoe,[3] Riggs,[4] Hammes [5]), and in October, 1919, it appeared almost simultaneously in Portland (House [6]), in Seattle and in Tacoma (Winslow [7]).

We have had an opportunity to observe twenty-seven cases, six of which occurred since the recent influenza epidemic and in which the clinical picture differed somewhat from those observed earlier.

The onset was usually gradual. . Severe diffuse headaches, disappearing rapidly after the first four to ten days, occurred eleven times in our series. Asthenia, lethargy, general muscle rigidity with masklike features (the paralysis agitans syndrome, usually without the tremor), any or all three of these symptoms manifested themselves in every case in a greater or less degree. Cranial nerve palsies were observed, the third and sixth were involved most frequently, and diplopia or blurred vision was a common complaint. The seventh nerve was involved unilaterally twice and bilaterally once, the tenth nerve once and the twelfth nerve in two cases. Eight cases gave no evidence of cranial nerve involvement at any time during the disease.

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1. v. Economo, C.: Encephalitis lethargica, Wien. klin. Wchnschr., May 10, 1917.

2. Abrahamson, I. Prevalence of Infectious Lethargic Encephalitis, Proc. New York Neurolog. Soc., J. Nerv. & Ment. Dis. **50**:61 (July) 1919.

3. Bassoe, P.: Epidemic Encephalitis (Nona), J. A. M. A. **72**:971 (April 5) 1919.

4. Riggs, C. E.: Epidemic Lethargic Encephalitis, Minnesota Med. **3**:49 (Feb.) 1920.

5. Hammes, E. M.: Lethargic Encephalitis (with Report of Twelve Cases), Minnesota Med. **3**:118 (March) 1920.

6. House, W.: Epidemic (Lethargic) Encephalitis, J. A. M. A. **74**:372 (Feb. 7) 1920.

7. Winslow, K.: Epidemic Lethargic Encephalitis (Nona) in Seattle, Northwest Med. **18**:209 (Oct.) 1919.

In seven cases the pupils did not respond to light or accommodation; in two the pupils were miotic, in one mydriatic, and in three irregular in size.

Partial atrophy of the hand muscles (right) was observed in one case; three cases manifested weakness and one definite paralysis of one arm. Tremor of variable amplitude and location occurred in five cases. Ticlike contractions of the facial or arm muscles were observed four times. Choreiform twitchings, hemiplegic and suggestive of Huntington's type, were marked in one patient. Another patient had two general convulsions in one day two weeks after the onset of the illness, followed by motor paralysis of the right arm which improved gradually.

Urinary retention, necessitating catheterization, was present five times. Involuntary urination or dribbling occurred in only two cases.

The temperature varied between normal and 103.4 F. Five patients had a normal temperature throughout, and although they presented a typical clinical picture, the disease ran an uneventful course and the patients made a satisfactory recovery.

The mental picture has been a variable one. Delusions and hallucinations occurred. Temporary disorientation and confusion were not infrequent. One patient presented the picture of a catatonic type of dementia praecox; another one developed a typical Korsakoff's psychosis; a toxic delirium was observed in four cases associated with a high temperature. Wilson [8] described a case in which typical "Witzelsucht" was manifested through the entire course of the illness. House [6] states that euphoria in a greater or less degree occurred in every one of his patients.

The deep reflexes have been either normal, increased or absent. The youngest patient was 14 years of age, and the oldest, 54. Eight of our patients were females and nineteen were males. Of the first twelve patients, six died. Of the remaining fifteen patients, all are still living. Judging from our observation, the clinical course was gradually becoming milder until the occurrence of our recent influenza epidemic (January and February, 1920). Since then the cases (six) have been of a very severe and more toxic type, although none have been fatal as yet.

In the shortest case entire recovery occurred within three weeks. The longest one in our series began in December, 1918. At present the patient is still lethargic, and has epileptiform attacks involving the left side of his face. Another case in our series began Sept. 16, 1919. The patient remained lethargic for more than two months, had a tem-

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8. Wilson, S. A. K.: Epidemic Encephalitis, Lancet **2**:7 (July 6) 1918.

perature between 100 F. and 103 F. for about one month. At present, he is able to sit up, feeds himself, takes some interest in his surroundings, but it unable to walk or talk.

The laboratory findings were quite uniform in our cases. There usually was a mild leukocytosis (average, 14,000). The spinal fluid gave a mild globulin test, a lymphocytosis varying between normal and fifty-seven per c.mm. The colloidal gold curve was of no aid in the diagnosis. In some cases, the most marked changes occurred in the syphilitic zone, in others in the meningitis zone and in several there was no change in any dilution. All blood and spinal fluid cultures were negative. No animal inoculations were done.

Tucker [9] reported two cases of lethargic encephalitis in which postmortem examination revealed some involvement of the hypophysis. His opinion was based on macroscopic examination alone, as no microscopic report was given. In our three cases which came to postmortem nothing abnormal was noted in the hypophysis on gross examination, but one of our patients presented a clinical picture suggestive of pituitary gland involvement.

REPORT OF CASES

CASE 1.—A male, 24 years of age, was first seen Nov. 25, 1919. His family and personal history are unimportant.

He contracted influenza in October, 1918. One week later he became drowsy and sleepy, and a few days afterward he became unconscious. This condition continued for about ten days, after which he gradually improved. Two weeks later he had a generalized epileptic attack which recurred at irregular intervals until Dec. 9, 1919. The attacks varied from four a day to one a month. They would commence with a "feeling of faintness," then the patient would become unconscious and have a generalized convulsion, bite his tongue and have involuntary urination. When he awakened he would feel tired and fall asleep for an hour or two. He, furthermore, described periods during which he would be confused mentally. At times he also had involuntary urination. He would be quite free from this for several weeks and then it would become very annoying for a week or so and clear up again. Mentally he is somewhat sluggish.

Since his influenzal attack, he has noticed that his breasts are enlarging, that he is losing the hair in his axillae and that he has to shave only every week or ten days, where formerly it was necessary to do this every other day. He has impairment of his sexual desire. His weight fluctuates considerably; within a week he would gain or lose ten pounds without any apparent reason.

The *neurologic examination* is negative, except for a slight Romberg. The fundi are normal; fields of vision normal. The physical examination shows a well built young man, with a dozen scant hairs on his chin only, although he has not shaved for six days. The hair on his head appears to be normal. In both axillae are a few scattered hairs. His pubic hair and his sexual organs are apparently normal. His breasts are somewhat enlarged and slightly tender on pressure. A roentgenogram of the skull is negative. There is no enlargement of the sella turcica.

9. Tucker, B. R.: Epidemic Encephalitis Lethargica or Epidemic Somnolence, or Epidemic Cerebritis with Report of Cases and Two Necropsies, J. A. M. A. **72**:1448 (May 17) 1919.

The *laboratory findings* are: hemoglobin, 80 per cent.; erythrocytes, 4,800,000; leukocytes, 7,900; differential count, normal; blood Wassermann, negative; blood pressure, 120 systolic, 70 diastolic. The spinal fluid was under normal pressure, gave a trace of globulin, two lymphocytes per c.mm., a negative Wassermann and a negative colloidal gold curve.

Under *treatment* with whole pituitary extract 2 grains three times a day, and luminal, ⅔ grain, three times a day, he has been free from attacks since Dec. 9, 1919, but has noticed no other change in his condition.

CASE 2.—This case was suggestive of a thalamic syndrome. A young woman, age 29, was seen in consultation with Dr. Goltz, Jan. 27, 1920. She gave a history of having had a severe chill Jan. 17, 1920, accompanied by severe headache, fever, vertigo and general malaise. Jan. 24, 1920, she complained of blurred vision, drowsiness and nervousness. She had a slight general tremor of both arms which was not present when she was seen three days later. At this time she complained of diplopia, drowsiness, stiffness in her extremities and difficulty in starting the flow of urine. Her face was masklike, she was lethargic and answered questions sluggishly. On examination, the left pupil was larger than the right, and it was irregular. There was no response to light or accommodation. There was a paralysis of the left internal rectus. The fundi were negative. The upper extremities were normal, the lower extremities rigid, all deep reflexes normal.

About February 1, she developed irregular choreiform movements of her left arm and leg. These also involved the left facial muscles and the left sternomastoid. The movements were irregular and jerky, simulating a Huntington's chorea. They were aggravated when the patient attempted to use either left extremity. Since February 15 this has become so marked in her left facial muscles that it was difficult to understand her. She protruded her tongue normally, but there was a slight tremor present. Her right side was entirely free from these movements and the posture of the right extremities was almost catatonic. Her muscle strength was good in all four extremities. The neurologic findings have remained the same.

The laboratory findings were: leukocytosis, 14,000; negative blood Wassermann; spinal fluid under normal pressure, gave a heavy trace of globulin, fifty-seven lymphocytes per c.mm. and a negative Wassermann. Urine negative.

The lethargic condition had entirely subsided by February 24, but the choreiform movements were marked and the patient complained of difficulty in going to sleep because of them. She had a temperature of 101 F. during the first week, which gradually became normal and has remained so. She has had difficulty in taking sufficient food and is gradually losing weight and strength.

Howe [10] describes very completely a thalamic syndrome in one of his cases of lethargic encephalitis.

Six cases of lethargic encephalitis seen during the past month have presented an onset somewhat different from the previous cases. There was more evidence of meningeal irritation and mental confusion. The following case was seen Feb. 16, 1920, in consultation with Dr. Sanford at Farmington, Minn.

CASE 3.—The patient was a farmer, age 52, with a negative family and personal history, except that he had an attack of pneumonia in November, 1918. About Feb. 2, 1920, he noticed a mild left conjunctivitis with severe pain in the eyeball. This gradually subsided, and within a few days he developed severe

10. Howe, H. S.: Thalamic Syndrome in Epidemic Encephalitis, Neurolog. Bull., N. Y. **2**:190 (May) 1919.

neuralgic pains in both occipital nerves. Soon after, this same condition extended into both arms, the pain being so severe that it was necessary to resort to morphin for relief. Two days later, he complained of similar pains in his lower extremities. These attacks of pain occurred frequently during the day and night. In the intervals the patient was quite comfortable.

About this time he became confused and disoriented, and during the night, he became quite delirious. His temperature was normal during the first week, but gradually increased until it was 102 F. at the end of two weeks. He also complained of blurred vision, and that if he looked to the right, the wall appeared at an angle and the pictures on the wall seemed to be at the foot of the bed. On the evening of February 15, he became drowsy and the next morning he was very lethargic, but could be aroused readily.

The *neurologic examination* was negative throughout.

The spinal fluid was under normal pressure, gave a trace of globulin, seven lymphocytes per c.mm., a negative Wassermann and a colloidal gold curve 1344210000. Since then he has developed a typical picture of lethargic encephalitis; his neuralgic pains have subsided, but he is still confused and delirious at night.

Our histopathologic studies have been based on the following three cases: [11]

CASE 4 (147).—Male, age 53, admitted Oct. 16, 1919, to the Neurologic Service, City and County Hospital, St. Paul, gave a negative family and personal history. Oct. 12, 1919, the patient complained of an acute coryza, severe headache, general malaise and joint pains. He began to wander around his home in an aimless manner. The following day he became drowsy and sluggish mentally, and soon after he became stuporous. He was disoriented, but answered all other questions intelligently. He was lethargic but could be aroused readily.

The *neurologic examination* showed the following: Pupils were moderately dilated and did not respond to light or accommodation. There was weakness of the right external and left internal rectus eye muscles. The fundi were negative. The face was masklike, but the patient could move all the facial muscles. He protruded his tongue with difficulty. The upper extremities were normal, but mildly spastic. The lower extremities showed absent knee and Achilles jerks, no Babinski, no spasticity.

Leukocytosis, 11,850, blood culture negative, urine normal, except for a trace of albumin. Blood Wassermann negative. Spinal fluid gave increased pressure, a trace of globulin, fifteen lymphocytes per c.mm., a negative Wassermann and a colloidal gold curve 2334300000. Repeated lumbar punctures gave similar spinal fluid findings. The patient progressively grew worse and died eighteen days after the onset of the illness.

CASE 5 (149) is of interest because of the involvement of the respiratory centers early in the disease. Male, age 45, admitted on the Neurologic Service, City and County Hospital, St. Paul, Oct. 29, 1919. His family and personal history were negative. October 15, the patient noticed that he felt weak, drowsy and wanted to close his eyes. He continued his work as a teamster for three days, until he went to sleep while driving his truck; fell down and injured his knee. He remained home for eleven days during which he "slept" most of the time. He also noticed difficulty in breathing at times. Patient was examined October 20; he was in bed motionless and with eyes closed. He could be aroused readily, answered questions, got up and walked around, and presented the typical gait and posture of a paralysis agitans. Occasionally, he would have

11. These three cases have been previously reported from the clinical standpoint by one of us (E. M. H.) in Minnesota Med. **3**:145 (March) 1920.

a general coarse tremor. At irregular intervals, he would get attacks of cogwheel respiration of from one to two minutes' duration, during which his respiration would go up to 72 per minute. He was markedly rigid.

Physical examination was negative, except for an atrophy of the left calf muscles, which patient stated he had had all his life. His pupils were normal. The light and accommodation reactions were sluggish and disappeared after three days. There was a paralysis of the right internal rectus. The face was masklike, but all movements were normal. All other cranial nerves were normal. All deep reflexes were normal, except for an absence of the left Achilles jerk.

Blood culture was negative, Widal negative, Wassermann negative; leukocytes, 12,200. Spinal fluid was under pressure, contained ten lymphocytes per c.mm., and a trace of globulin, but was otherwise normal. His temperature varied between 100 and 102 F.; his pulse was around 130; his respirations varied between normal and 72. His stupor gradually deepened and he died Nov. 9, 1919.

CASE 6 (151).—Male, age 23, was admitted on Dr. A. Hoff's medical service, City and County Hospital, St. Paul, Nov. 16, 1919, with a diagnosis of suspected typhoid. A lethargic encephalitis was suggested, and Dr. Hoff kindly permitted one of us (E. M. H.) to see the patient. His family and personal history were negative. About November 9, he began to feel drowsy and weak. Soon after he had two severe attacks of epistaxis. About November 12, he developed marked photophobia, also a slight general muscle rigidity and he became stuporous. We first saw the patient November 18; he was drowsy but could readily be aroused, and he answered questions coherently. His mental condition was normal. He could not open his eyes because of marked photophobia.

Neurologic examination showed the following: Pupils equal and responded to light and accommodation. He had a paresis of the left internal rectus. All other cranial nerves were normal. All deep reflexes were normal. He had a positive right Babinski.

Blood culture was negative, Widal negative, Wassermann negative; leukocytosis, 17,000; urine normal. Spinal fluid was normal, except for a positive globulin and fifty-four lymphocytes per c.mm. November 19, he seemed confused and disoriented and developed a typical mental picture of a Korsakoff's psychosis. He died Nov. 21, 1919.

PATHOLOGY

The pathologic findings in the three cases we have studied microscopically correspond in the main to the other cases described in the literature (Bassoe,[3] Bassoe and Hassin,[12] Wegeforth and Ayer,[13] Neal,[14] Calhoun,[15] special article in *Journal American Medical Asso-*

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12. Bassoe, P., and Hassin, G. B.: A Contribution to the Histopathology of Epidemic ("Lethargic") Encephalitis, Arch. Neurol. & Psychiat. **2**:24 (July) 1919.

13. Wegeforth, P., and Ayer, J. B.: Encephalitis Lethargica, J. A. M. A. **73**:5 (July 5) 1919.

14. Neal, J. B.: Lethargic Encephalitis, Arch. Neurol. & Psychiat. **2**:271 (Sept.) 1919.

15. Calhoun, H. A.: Histopathology of brain and Spinal Cord in a Case Presenting a Postinfluenzal Lethargic Encephalitis Syndrome, Arch. Neurol. & Psychiat. **3**:1 (Jan.) 1920.

ciation,[16] Marinesco,[17] Netter,[18] von Economo,[19] and Vaughan [20]). Our findings consist in congestion, edema, petechial hemorrhages, pigmentation, perivascular and diffuse infiltration of round cells, proliferative changes in the endothelial and interstitial tissues, and degenerative changes in the nerve cells and myelin sheaths. The whole central nervous system, including the meninges, shows evidence of involvement in the disease process, but the most marked changes are uniformly in the lenticulo-striate complex, the midbrain, pons and medulla. No extensive review of the literature on the pathology of lethargic encephalitis is contemplated in this report, but differences noted in our cases as compared with some of the others reported will be brought out in the description of the histopathology.

At the time of necropsy no gross lesions were noted in the central nervous system, aside from the fact that the meningeal vessels were markedly congested in Case 151 and moderately congested in Case 149. No recognizable hemorrhages or areas of softening were encountered. No pathologic changes having any significance in connection with this report were noted in other parts of the body. The postmortem examinations were performed by Dr. Kramer, pathologist at the City and County Hospital of St. Paul. The brains and cords (no cord received from Case 147) were delivered to us in 10 per cent. liquor formaldehydi.

Blocks of tissue were taken from various areas of the cerebral and cerebellar cortices, the basal ganglia, midbrain, pons, medulla and cord. Sections from these blocks were stained with thionin, Weigert's myelin sheath stain, Marchi's stain, Bielschowsky's stain, sudan III, stains for hemosiderin, and Dominici's stain (toluidin, Orange G, and eosin—an especially good stain for the study of free cells in sectioned material).

For the most part, aside from congestion of the vessels, the meninges show only very mild involvement in the inflammation. Occasional areas are to be seen in which there is a slight increase in the number of nuclei in the meninges, due to an infiltration of small round cells of the same type as will be described later in the brain substance. In one case (151), the sections passing through the attach-

16. Special Article: Epidemic or Lethargic Encephalitis (Nona), J. A. M. A. **72**:794 (March 15) 1919.

17. Marinesco, G.: Contribution à l'étude de l'histologie pathologique de l'encéphalite léthargique, Bull. de l'Acad. de méd., Par. **80**:411 (Nov. 5) 1918.

18. Netter, A.: L'encéphalite léthargique épidémique, Bull. de l'Acad. de méd., Par. **79**:337 (May 7) 1918.

19. v. Economo, C.: Wien. klin. Wchnschr. **31**:850 (July 25) 1918.

20. Vaughan, V. C.: Encephalitis Lethargica, J. Lab. & Clin. M. **4**:381 (April) 1919.

ment of the trigeminal nerve show marked perivascular and diffuse infiltration of these and other cells together with hemorrhage into the subarachnoid spaces in the region of the fifth nerve root. The changes at this point involve not only the meninges, but also the nerve trunk itself and the underlying region of the pons (Fig. 1, B and C). This area presents a decided departure from the picture of the meninges seen in any of the other sections from our cases. It appears that the meninges are even less involved in our cases than in the majority of those reported in the literature.

In the cerebral cortex of all three cases there is marked congestion of the vessels. There is slight diffuse and perivascular infiltration of small round cells (lymphocytes and plasma cells) with an evident tendency for these cells to collect especially about the bases of the pyramidal cells (Fig. 2, B). While examples of satellitosis are fairly common, no true neuronophagia is to be seen; that is, there is no evidence of actual destruction and phagocytosis of the cortical cells by the satellite cells, none of these cells are intracellular within the nerve cell bodies, the cortical cells are in a state of good preservation, showing only mild chromatolytic changes. No hemorrhages are seen within the cortical layers. No proliferative glial or endothelial changes have been noted.

The cerebellar cortices of Cases 147 and 149 appear quite normal except for a rather marked congestion of all the vessels. In Case 151, however, the molecular layer of the cerebellar cortex shows a decided diffuse infiltration of small round cells (lymphocytes) along with the congestion. Deep in the sulci of the cerebellum in this case the vessels are surrounded by scattered round cells. There are no noteworthy changes in the cells of Purkinje; our cases do not confirm the changes described by Calhoun [15] in regard to these cells. The granular cell layer appears normal in each of the three brains.

The thalamus, caudate nucleus, globus pallidus, putamen, midbrain, pons and medulla all show great uniformity in their pathology in all of our cases; hence they can be discussed together.

Perivascular infiltration of round cells about the congested vessels is the most evident change noted. These cells have invaded the walls of the vessels to a very marked extent, leaving the perivascular space of His relatively free, however (Fig. 3, A). Diffuse infiltration of these cells into the surrounding tissues is also marked. On high power examination it is seen that the majority of these cells are slightly larger than erythrocytes, and are made up of a rounded nucleus containing relatively large masses of chromatin arranged more or less wheel-like around the inside of a definite nuclear membrane, and a small amount

of, or no visible cytoplasm (Fig. 4, A). It is probable that these cells should be classified as small lymphocytes rather than plasma cells, as Bassoe and Hassin [12] have suggested. That there are plasma cells among the infiltration cell types is not at all to be doubted, however, for we have found a number of cells with relatively large amounts of cytoplasm, eccentric, rounded nuclei containing chromatin granules with a very definite wheellike arrangement and often a vacuole or vacuoles bordering on the nucleus (Fig. 4, A and B, pl). Plasma cells in our cases are distinctly in the minority, being very scarce perivascularly, and only occasionally found scattered in the tissues.

Another type of cell making up a part of the infiltration, much less numerous, however, than either the lymphocytes or plasma cells and most in evidence in the area of infiltration and hemorrhage around the origin of the fifth nerve in Case 151, is that which might be called a macrocyte, an endothelial cell or a large mononuclear cell, depending on who might be describing it. This cell is considerably larger than the lymphocytes, contains a large, rather irregular (sometimes spherical) nucleus whose chromatin material is not very dense and does not tend towards any particular arrangement about the nuclear membrane which is more delicate than that of the lymphocytes or plasma cells. The cytoplasm stains purplish (neutrophilic) with Dominici's stain and is rather granular and sometimes vacuolated. These cells are certainly phagocytic for many of them contain nuclear and other cell debris (Fig. 4, A, and Fig. 1, B). Polymorphonuclear leukocytes are absent, except in such places as contain hemorrhages; here they are not present in any great numbers and probably have simply escaped from the blood stream along with the extravasated erythrocytes. The lymphocytes and plasma cells are situated not only perivascularly, but have also wandered out into the brain substances so that in the affected areas a low power examination gives one the impression of a very marked increase in the number of nuclei in the field (Fig. 3, A).

In the basal ganglia of one case (151) is a small abscess large enough to be seen in the stained section with the naked eye, consisting almost exclusively of lymphocytes. The tissues surrounding it are infiltrated with lymphocytes and are definitely fragmented. Fortunately, we obtained practically serial sections through this region which show that the abscess has not been confused with perivascular infiltration as no vessels larger than precapillaries are in that vicinity (Fig. 3, C).

Hemorrhage is not a marked feature of the pathology in any portions of the central nervous system we have studied. Small hemorrhages, or, at least, areas in which red blood corpuscles are to be seen

in the perivascular space of His are not at all uncommon in the regions in which pathologic changes are marked — basal ganglia, midbrain, pons and medulla — and are altogether absent elsewhere (Fig. 3, B). Neal [14] states that "Frequent small and occasional large extravasations of blood are seen anywhere, but especially in the gray matter." In view of the evident vascular injury it would certainly be easy to understand how sizable hemorrhages could take place, but none of noteworthy size have been observed in any of our sections. Such hemorrhages as we have seen must have occurred shortly before death as the erythrocytes are in a state of good preservation and there is no blood pigment out in the tissues; stains for hemosiderin are negative.

Separation of the tissues of the brain in the more severely injured areas, giving the appearance of much dilated tissue spaces, is a constant feature of our sections. This looseness of the tissue meshwork is taken by us to be evidence of a marked edema, though the possibility of artifacts has been constantly kept in mind. The occurrence of this change in the affected areas and its absence in the relatively normal areas makes us feel safe in stating that there is edema present (Fig. 3, A; compare Fig. 4 and Fig. 2, A, with Fig. 2, B and C).

Glial proliferation in the affected regions is not marked at first glance. As the slides are studied, however, it appears that there is a definite increase in the number of glial nuclei. Furthermore, young types of glial cells are not uncommon with their relatively large nuclei and definitely increased cytoplasm. In one section (Fig. 4, C) an undoubted example of mitosis in a glial cell is present. No free cells of definitely glial origin have been found. Proliferative changes in the endothelial cells are also not marked in the central nervous system with the exception of the region of the meninges about the origin of the fifth nerve in Case 151. Here one finds numerous vessels slightly larger than capillaries in which the endothelium is made up of cells with marked increase in their cytoplasm and large rounded or oval, usually vesicular nuclei. Since the nucleus and cytoplasm of these endothelial cells simulate very closely the appearances in the macrocytes, and since the macrocytes are definitely phagocytic, we feel that these large free cells are undoubtedly endothelial in origin (Fig. 1, B).

Various changes are noted in the nerve cell bodies located within the severely affected areas. In these regions it is exceptional to find a normal neuron; they all show evidences of one or another type of degeneration. Examples of satellitosis about the nerve cells are very common, those of actual neuronophagia considerably less frequent, though present (Fig. 2, B and C). The satellite cells are indistinguishable in their morphology from the lymphocytes described above. Chromatolysis is the rule in these localities, usually evidenced by loss

of Nissl bodies around the nucleus and collection of the remaining tigroid substance about the periphery of the cell (Fig. 2, A). The nucleus of the cell may be relatively clear and swollen or it may be somewhat darker and shrunken. Some of the nerve cells are vacuolated (Fig. 2, A); they are seldom actually fragmented. Most of them show an apparent, if not an actual decrease in the number of their processes. Pigmentation of the nerve cells is a marked feature of all the affected areas. The pigment is extremely abundant in some of the cells, completely filling the cell body and even obscuring the nucleus. The pigment granules are small, rounded, regular and yellowish brown in all the sections excepting those stained by Sudan III when they take the red color of the stain; therefore, they are lipochrome granules. The pigment is located not only within the neurons but occurs free in the interstitial tissues and also within the cytoplasm of the glial cells (Fig. 4, B). Stains for hemosiderin are negative even in the presence of hemorrhages; hence this pigment is not a derivative of the blood pigments.

Weigert sections show no involvement of the long tracts in the brain and cord. In the nuclei within the affected areas, however, the finer myelinated fibers show definite evidences of degeneration. Some of the myelin sheaths are actually fragmented; others show the peculiar swelling and knobbing characteristic of early myelin sheath changes. These changes are particularly noticeable within the nucleus of the third nerve (Fig. 1, A), but are found even in the projection fibers of the cerebral cortex.

The spinal cord is involved to the extent of considerable congestion, some increased pigmentation of the nerve cell bodies and fairly common examples of chromatolysis.

There are no changes of any significance in the ependyme of the ventricles of the brain or the central canal of the cord.

It is worthy of mention that in the rootlet of the trigeminal nerve in Case 151 there is very marked perivascular and some diffuse infiltration of lymphocytes (Fig. 1, C). We have seen no inflammatory changes in any of the other nerve rootlets.

DISCUSSION

The laboratory findings in our cases have thrown no light on the etiology of lethargic encephalitis. This is in accord with most investigators. v. Wiesner [21] cultured a gram-positive diplococcus from a monkey which had previously been inoculated subdurally by an emul-

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21. v. Wiesner, P. R.: Die Aetiologie der Encephalitis lethargica, Wien. klin. Wchnschr. **30**:933, 1917.

sion of the brain and cord from one of v. Economo's patients. Strauss, Hirshfeld and Loewe [22] also successfully inoculated monkeys with an emulsion of the human brain and produced the characteristic lesions of lethargic encephalitis. In a later report they state that they have isolated a gram-positive organism resembling that described by Flexner and Noguchi in poliomyelitis.

Although no definite relationship has been established between influenza and lethargic encephalitis, the clinical evidence is very suggestive for every epidemic of lethargic encephalitis has been preceded by a pandemic of influenza.

Neal,[14] Bassoe and Hassin,[12] and Calhoun [15] have pointed out the similarity pathologically between lethargic encephalitis, acute anterior poliomyelitis and trypanosomiasis, and have considered the possibility of a common etiology, but have been able to reach no definite conclusions.

SUMMARY AND CONCLUSIONS

1. No definite etiologic factor has yet been established in lethargic encephalitis. The relationship clinically to influenza is very suggestive.

2. Although the general symptomatology is profound, the localizing symptoms are not so marked as the widespread pathologic findings would lead one to expect.

3. Asthenia, lethargy, muscle rigidity and cranial nerve involvement are the outstanding features of lethargic encephalitis clinically.

4. Pathologically, the picture is an inflammation of the brain and cord characterized by a perivascular and diffuse infiltration of lymphocytes especially in the basal nuclei and gray matter of the brain stem.

22. Strauss, I., Hirshfeld, S., and Loewe, L.: Studies in Epidemic Encephalitis (Encephalitis Lethargica), New York M. J. **109**:722 (May 3) 1919.
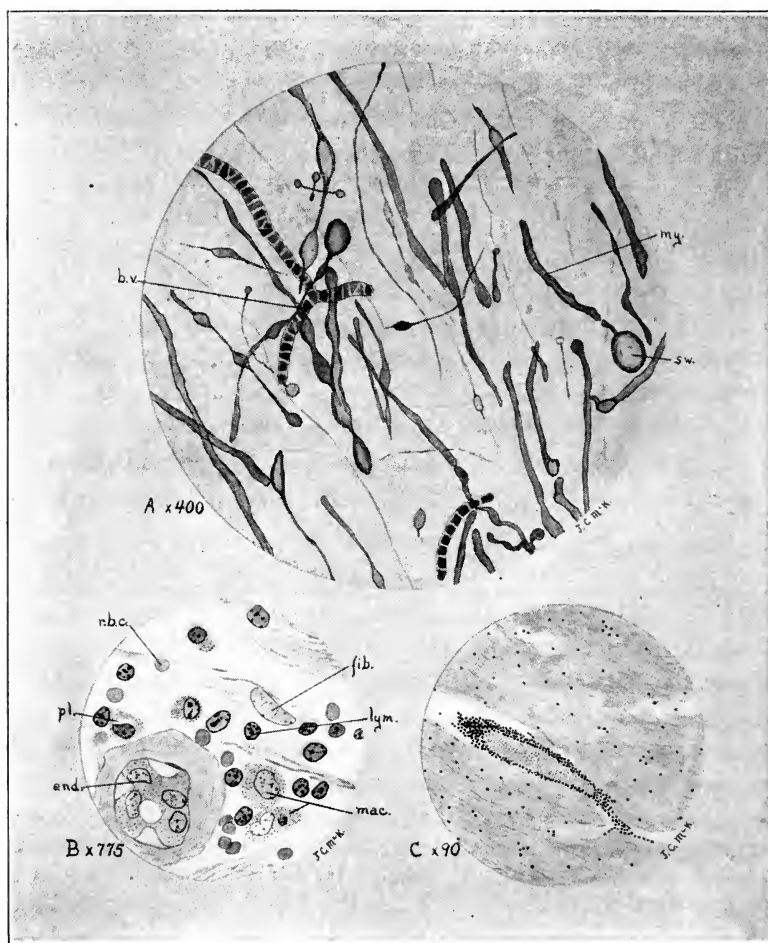
Fig. 1.—A. $\times$ 400. Nucleus of oculomotor nerve in Case 151 stained with Weigert's myelin sheath stain. Knobbing and fragmentation of the myelin sheaths. b. v., blood vessels; my., myelin sheath fragmented; sw., swelling or knobbing of the same sheath. B. $\times$ 775. Meninges near the attachment of the fifth cranial nerve in Case 151. Swollen endothelial cells still attached to a vessel wall, apparently ready to break loose and give rise to macrocytes. Hemorrhage and infiltration. end., swollen endothelial cells; fib., fibroblast nucleus; lym., lymphocyte; mac., macrocytes, one of them containing cell debris; pl., plasma cell; r.b.c., erythrocytes in the subarachnoid spaces. C. $\times$ 90. Perivascular infiltration in the root of the fifth nerve in Case 151.
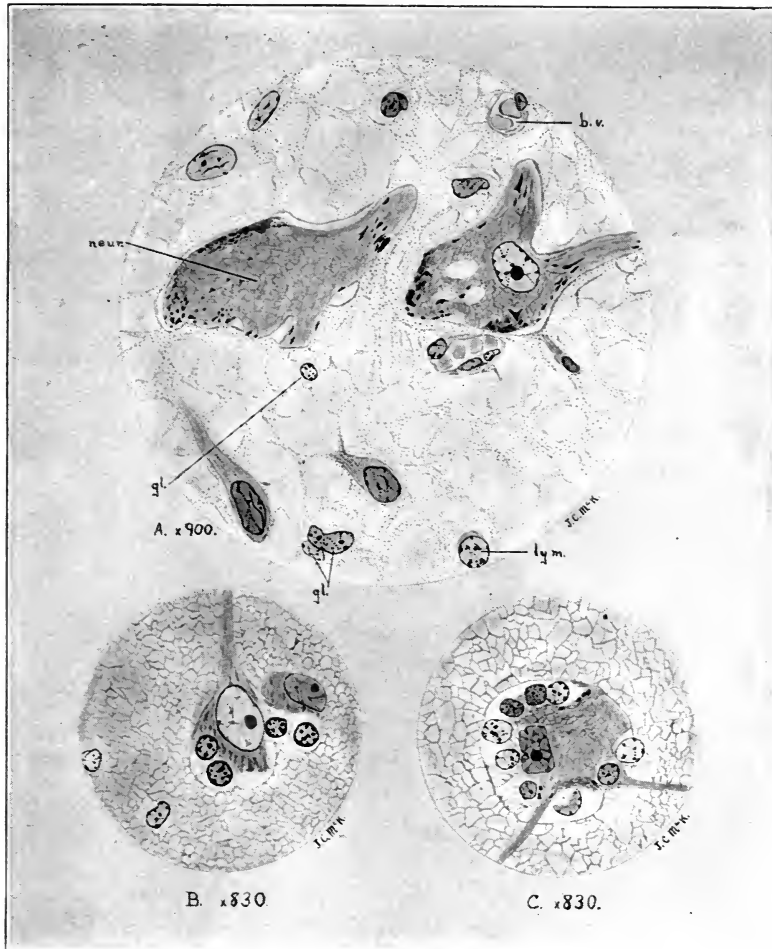
Fig. 2.—A. ✕ 900. Basal ganglia from Case 149. Chromatolytic, swollen nerve cells, one of which is vacuolated. b.v., blood vessel; gl., glial cell; lym., lymphocyte; neur., neuron. B. ✕ 830. Cortex from Case 147. Satellitosis about the bases of two pyramidal cells. C. ✕ 830. Basal ganglia from Case 151. Neuronophagia. Chromatolytic ganglion cells with pyknotic nucleus.
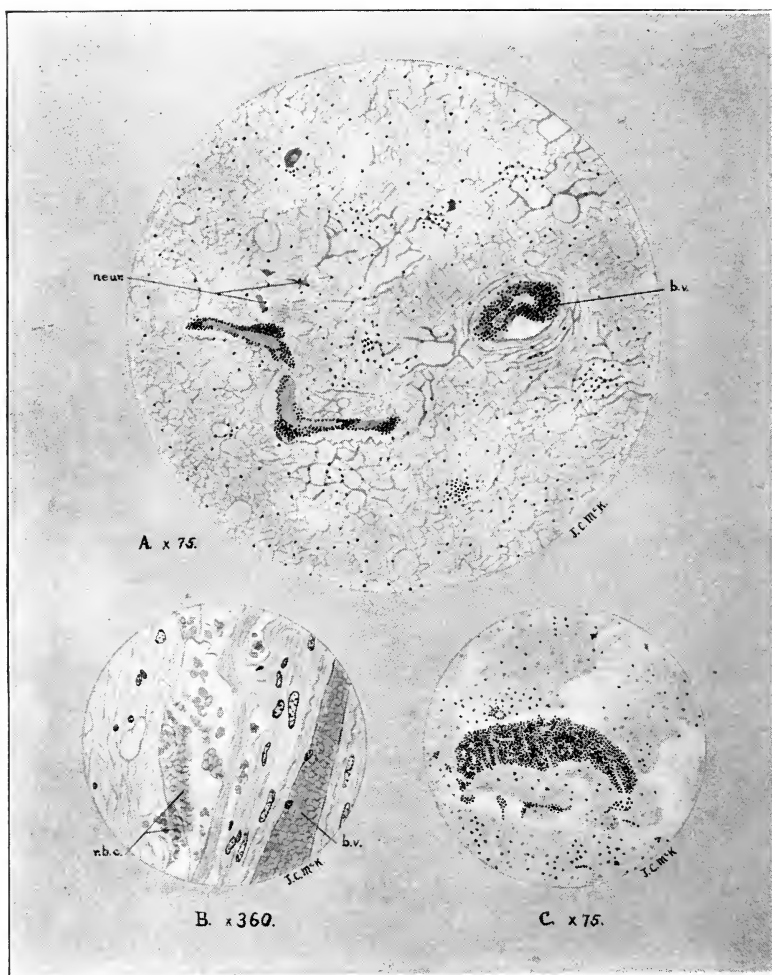
Fig. 3.—A. $\times$ 75. Midbrain from Case 147. Perivascular and diffuse infiltration of lymphocytes. Marked edema. Satellitosis about the nerve cell bodies. b.v., blood vessel; neur., neurons with satellite cells. B. $\times$ 360. Basal ganglia from Case 147. Small hemorrhage about a vessel. b.v., blood vessel; r.b.c., extravasated erythrocytes in perivascular space of His. C. $\times$ 75. Basal ganglia from Case 151. Small abscess made up of lymphocytes. Fragmentation of the surrounding tissues.
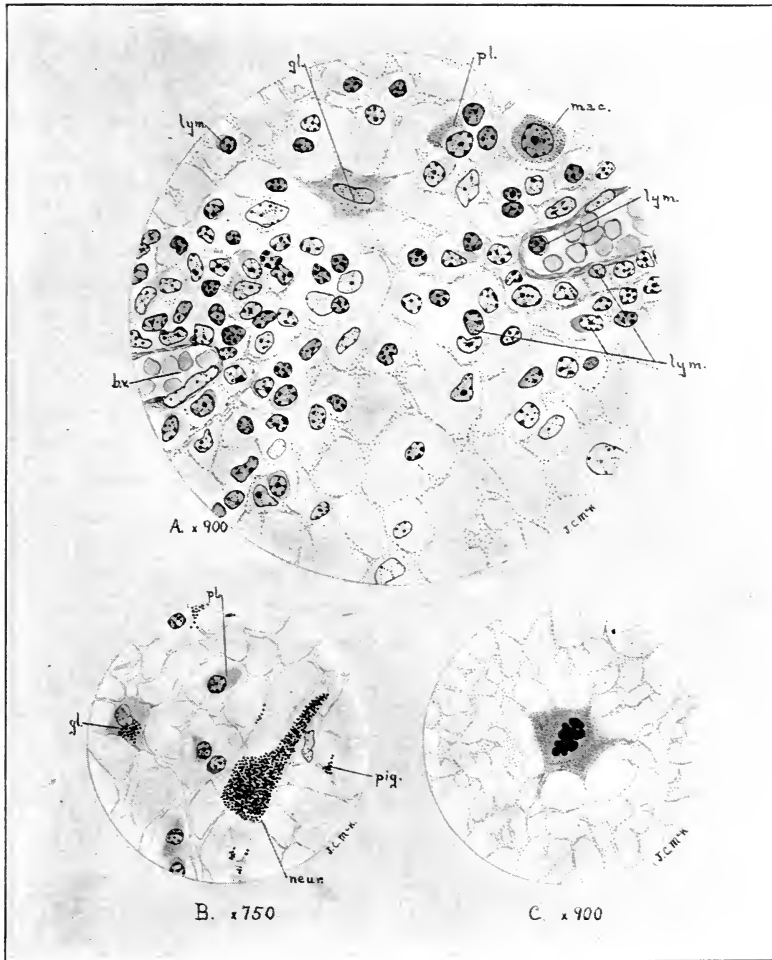
Fig. 4.—A. × 900. Pons from Case 149. Cell types making up the infiltration. b.v., blood vessel; gl., glial cell; lym., lymphocyte; mac., macrocyte; pl., plasma cell. B. × 750. Midbrain from Case 147. Pigment granules in a nerve cell body, in a glial cell and free in the tissues. gl. glial cell; neur., neuron filled with pigment; pig., pigment granules; pl., plasma cell. C. × 900. Basal ganglia from Case 151. Mitosis in a glial cell.

TRENCH FEVER *

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Disease is the accomplice of war. To the uninitiated, at first glance, it seems that the chief wastage of man power in armies is produced by weapons of the enemy; to the initiated, on the other hand, it is well known that the wounds produced by bacteria are as fruitful a source of disability as those caused by bullets. One reason for this attitude on the part of the casual observer is that the injuries of battle are more spectacular than those of disease. They are more unusual, both in their mode of production, and in the manner in which they respond to treatment. The care of the wounded often yields striking results. The humanitarian instincts, aroused by the fact that the injuries were received as a direct result of sacrifice, properly lead to the building up of an intricate organization for the care of the wounded. The problems must be solved largely in the actual presence of war. Sickness, on the other hand, is more easily tolerated because it is the lot of most men to suffer illness. The problems of disease are always with us; most of those presented by war have been studied in times of peace. Almost in direct proportion to the rate at which a given disease causes fatalities, in contradistinction to casualties, are effective prophylactic measures studied and put into effect. The antivenereal disease campaign in our own army is a striking exception to this statement. The prophylaxis of typhoid fever and smallpox was more effective than that of dysentery or the pyodermias. It may be urged that the measures for preventing the first two diseases are more easily applied in war. This is true; but had the prevalence of the fatal disease, typhus fever, been as great as that of the nonfatal, but disabling affection, trench fever, no doubt more effective measures would have been early instituted for combating it.

The complete ignorance of the existence of such a disease as trench fever, with the consequent lack of knowledge as to its mode of spread, made it impossible to apply prophylactic measures until this information was available. A very real impediment to the study of a disease during war is that the patients are rarely under the same observers or group of observers during the entire course of their illness. This was especially true during the first part of the recent war, before the lines had become stabilized and hospitals were stationed close enough to the front to permit the retaining of the sick for longer periods.

For these reasons it was not generally recognized until the spring of 1915 that a hitherto unknown disease was fairly widespread among the combatant troops. At this time, medical officers in both the British and the German armies almost simultaneously noticed a five or six day relapsing fever in many patients who complained of severe and persistent pains in the shins. Graham,[1] Herringham[2] and others saw many examples of this condition among British troops from the trenches but not among the troops in the rear; so the name of trench fever was applied. His[3] and Werner[4] saw their first cases on the east German front in Poland and Wolhynia. The former applied the term Wolhynian fever to the disease because of the supposed source of the infection; the latter used the term five day fever because of the interval between relapses. Because of the almost simultaneous appearance of cases on the two fronts it is difficult to determine the original source of the infection; but Grätzer,[5] a battalion medical officer in the Eighty-Fourth Austrian Infantry Regiment, states that he had observed cases among soldiers under his care since the winter of 1914. He gave a very good description of the malady; and because of its increase in winter and when crowding of the soldiers was necessary, he attributed the spread to some insect vector. He saw his first cases when his regiment was on the Nida, and learned from the inhabitants of that region that a similar condition was known to them before the war. Franke[6] also states that he recognized the disease as having occurred in Lemburg in previous years, when it was known as influenza with relapses. It seems, therefore, from the evidence at hand, that the original source of the infection was somewhere in Russia, and that the disease was spread to all of the battle fronts in Europe by German and Austrian troops as they moved from one area to another.

It was early noted by some observers that an enlarged, hard spleen, often accompanied by perisplenic tenderness, could be demonstrated in many of the patients. The outstanding features of typical cases were, however, the sudden onset with marked febrile reactions, headache and general body pains, closely resembling the onset of influenza, but followed in a few days by pain and tenderness in the shins, and a spiky type of relapsing fever. There were many patients who complained of painful shins, especially at night, but in whom there was no history of an abrupt onset, or of a distinct febrile bout. Various

1. Graham, J. H. P.: Lancet **2**:703, 1915.
2. Herringham, W.: Quart. J. Med. **9**:429, 1916.
3. His, H.: Berl. klin. Wchnschr. **53**:738, 1916.
4. Werner, H.: München. med. Wchnschr. **63**:402, 1916.
5. Grätzer, A.: Wien. klin. Wchnschr. **29**:295, 1916.
6. Franke, M.: Wien. klin. Wchnschr. **30**:45, 1917.

explanations, such as long marches, flat feet, standing in mud and water, rheumatism or myalgia were suggested to account for these unusual pictures. In still other patients with similar symptoms, the pyrexia was continuous, resembling that of typhoid or paratyphoid fever, or intermittent like that of sepsis.

Much confusion in diagnosis arose from the presence of so many patients having certain symptoms in common, yet presenting, on the other hand, so many individual variations. In fact, it was so difficult to establish a normal or typical picture of the disease that the terms P. U. O. (pyrexia of undetermined origin) or influenza were applied in many instances.

The ignorance of the existence of atypical forms of trench fever, the practical impossibility in many cases of making a positive diagnosis, and the great difficulty in establishing adequate sanitary measures during war of movement, were all factors that resulted in the infection being widespread before the disease had become recognized as a separate entity. A serious study to determine its nature was soon undertaken by investigators on both sides of the line. The first extensive report was that of McNee, Brunt and Renshaw,[7] who used as experimental subjects British soldiers who had volunteered for inoculation. These workers showed that the virus of the disease was contained in the whole blood and that it could be transferred from man to man by intravenous or intramuscular injection. In their experiments the plasma or serum obtained from infectious blood did not contain active virus unless hemoglobin tinged. The red blood cells, on the other hand, were infectious, even after five washings. Material known to contain virus was not infectious after passage through a Berkefeld filter; but in spite of this fact these workers were unable to demonstrate microscopically any micro-organism. This work, unfortunately, was interrupted before it was shown conclusively that trench fever was not a modified form of typhoid or paratyphoid fever, and before it had been established that the infection was transmitted by some insect vector. In spite of the questions that were left undecided, the observations of McNee, Brunt and Renshaw stand as the first important contribution to the nature of this disease. They showed that the inoculation of blood from a patient with the short form of fever, might result in infection showing a prolonged course, with spiky relapses every fifth day; the essential unity of a disease with multiform manifestations was therefore established.

In the year following this work, there were many unconfirmed reports from German workers, that they had been able to transmit

7. McNee, J. W., Brunt, A., and Renshaw, E. H.: Brit. M. J. **1**:295, 1916.

the infection to animals. Jungmann and Kuczynski [8] claimed to have produced a fatal infection in mice; and Strisower [9] reported that both cats and mice succumbed to a fatal infection following inoculation with blood from trench fever patients. The animals did not present a clinical picture similar to the disease in man; nor were they successfully inoculated through several generations. Most workers agree, however, that it is impossible to transmit the typical disease to the ordinary laboratory animals; although extensive experiments have not been attempted with the higher apes. For this reason, all experimenters have found it necessary to resort to the inoculation of human volunteers in order to obtain any definite, useful information in reference to the nature and mode of transmission of the infection. Werner and Benzler [10] successfully inoculated themselves by means of instramuscular injections of blood from trench fever patients. Six months later Werner allowed himself to be bitten by lice that had previously fed on trench fever patients, and after an incubation period of eight weeks developed a mild illness that was diagnosed as Wolhynian fever. Kuczynski [11] also contracted the disease after being bitten by supposedly infected lice. In all of the experiments carried on by the German workers there is no mention that the inoculated subjects had been isolated from other cases of trench fever, or that special efforts were made to elimiate other sources of infection. It is a well known fact that doctors, nurses and attendants in military hospitals where the disease was prevalent were specially subject to accidental infection. Furthermore, there is little evidence to show that the stocks of lice were free from infection before use in the experiments. Davies and Weldon,[12] of the English army, allowed themselves to be bitten by lice immediately after an infecting feed on trench fever patients; the lice were originally collected from soldiers. One of them developed trench fever twelve days later. The same criticism that has just been made of the German work can equally well be applied to their experiment. It is not intended to underestimate the efforts of any of these workers, but rather to point out that the results were not sufficiently conclusive to warrant the undertaking of extensive prophylactic measures along any particular line.

Late in 1917, Pappenheimer and Mueller [13] of the Presbyterian Base Hospital of New York succeeded in transmitting the disease to one

8. Jungmann, P., and Kuczynski, M. H.: Deutsch. med. Wchnschr. **64:** 359, 1917.

9. Strisower, R.: München. med. Wchnschr. **65:**476, 1918.

10. Werner, H., and Benzler, F.: München. med. Wchnschr. **64:**695, 1917.

11. Kuczynski, M. H.: Reported in Jungmann, P.. Monograph, loc. cit.

12. Davies, F. C., and Weldon, R. P.: Lancet **1:**183, 1917.

13. Pappenheimer, A. M., and Mueller, J. H.: Reported in American Red Cross Committee Report, loc. cit.

of three volunteers by allowing lice to feed, first, on several trench
fever patients and then on the volunteers. In their experiments, the
volunteers were kept carefully isolated. Unfortunately, the patient to
whom the disease was transmitted suffered from a complicating femoral
phlebitis. I saw him on several occasions, and have little doubt that
he had true trench fever. Here again, it could not be asserted posi-
tively that the lice were not infected before they fed on the trench
fever patients.

These isolated observations were all highly suggestive, but awaited
confirmation by more extensive experiments before they could be trans-
lated into active effort. In fact, there were negative experiments,
such as those recorded by Sundell and Nankivell,[14] and many reports
of patients who denied having been bitten by lice, that threw doubt
on the louse transmission hypothesis. Epidemiologic studies were highly
unsatisfactory because of the constantly changing population in most
military units. The proof that rats were the active agents in the
transmission of spirochetal jaundice naturally suggested that trench
fever might be spread in a similar manner. It is evident that it was
impossible to frame any effective program to combat the spread of the
disease in the face of so much conflicting evidence and opinion.

In the meantime accumulated evidence showed that trench fever was
one of the largest sources of wastage of man power in the fighting
armies. It is estimated that during 1917 and 1918, before the
influenza epidemic, it was the cause of from one-fifth to one-third
of all of the cases of illness in the British armies in France. The
German reports indicate that this disease was responsible for at least
one-fifth of the illness in the armies of the Central Powers. Although
the illness was never fatal, it resulted in prolonged disability. A report
from the Boulogne Base [15] of the British army shows that patients with
trench fever were unfit for military duty on an average of from
sixty to seventy days, and that in addition at least 10 per cent. of
them became semipermanent invalids.

This is a brief sketch of the state of our knowledge at the time
of the formation of two commissions to study the disease more care-
fully. It was perfectly evident that to obtain the most accurate
information it was necessary that the experimenters should be free
from the manifold duties of an army medical officer. The conditions
under which members of these commissions worked satisfied these
requirements. The British Commission in London had the advantage
of a permanent hospital and laboratories, and the assistance of the
workers of the Lister Institute. Volunteers for inoculation and fresh

14. Sundell, C. E., and Nankivell, A. T.: Lancet **1**:399, 1918.

15. Elliott, T. R., Lewis, D. S., Thursfield, J. H., Jex-Blake, A. J., and
Foster, M.: Lancet **1**:1060, 1919.

cases of the disease were not so available as in France. It was possible to conduct the experiments in a more leisurely manner, and thus to study in more detail the problems as they arose.

The commission [16] formed under the auspices of the American Red Cross, on the other hand, started its work under field conditions. Later it was necessary to move the laboratory, patients and personnel to Paris, where better facilities were available. We were compelled to solve the problem as quickly as possible. We had the advantage of starting the work in a place where numerous examples of fresh infection of the disease were available, and where the Trench Fever Commission of the British Expeditionary Force had been carrying on clinical studies for some time. The advice of experienced observers was, therefore, available both in the selection of suitable patients from which to obtain the virus, and in the decisions as to the nature of the disease produced. Every facility at their disposal was offered by both the British and American military and medical authorities. The members of the commission were chosen because they could carry out their particular part of the work with the least possible delay. Captain Peacock was loaned by the R. A. M. C. to help in the entomologic work, because of his previous experience with the life and habits of insects.

These details are related in order to make clear the conditions under which the answers to the various problems were obtained. Throughout the entire period of our work there was the closest cooperation between all of the interested organizations. As fast as positive results were obtained by one commission they were made known to the other, and thus much time was saved to both. It is only natural that different lines of investigation should have been followed by different workers, and somewhat divergent results obtained; but in the main facts the two commissions agree. This communication, therefore, will consist largely of a résumé of the work of these two bodies.

Before proceeding, however, it is well to credit the volunteers for the large part they played in the success of the experiments. Probably in the investigation of no other disease have so many men submitted themselves to artificial inoculation. Even though they could be reasonably sure that their illness would not be fatal, they knew that they would suffer much pain and incapacity for an indefinite period. In spite of this knowledge, both our own soldier volunteers, and the British civilians who offered themselves, underwent the trying experience with the greatest fortitude. As a direct result of their sacrifice,

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16. The Commission consisted of Majors Strong and Opie, Captains Macneal, Baetjer and Pappenheimer, Lieutenant Rapport and myself, all members of the Medical Corps of the U. S. Army, and Captain Peacock, an entomologist from the Royal Army Medical Corps.

much information was obtained that led to the institution of measures for the prevention of the spread of trench fever in both military and civilian population.

It will be recalled that although McNee, Brunt and Renshaw [17] had fairly well proven, by human transmission experiments, that trench fever was a disease entity related in no way to the typhoid fever group, there were many clinicians who still held that the malady was a form of enteric fever modified by the immunity that had been induced in soldiers by protective inoculations. There were many cases in the British enteric fever hospitals diagnosed by means of agglutination reactions as typhoid or paratyphoid fever that presented clinical pictures resembling trench fever in almost every respect. One of our first problems was, therefore, to confirm McNee's observations, and to establish definitely that the patients with whom we were working were not suffering from any other disease than trench fever. More than thirty volunteers [18] were inoculated with blood or some fraction of blood. In all of the original patients from whom the virus was obtained, as well as in those that developed the disease as a result of inoculation, it was proven by bacteriologic examination that no known bacterium played any etiologic rôle in the condition under consideration. Like McNee and his co-workers, we found that the whole blood contained the virus, but in contradistinction to their findings, we determined that the plasma, obtained from citrated blood, was always infectious. In four out of five experiments the incubation period in the patient inoculated with citrated plasma was shorter than in control patients inoculated with the whole blood. It seemed, therefore, that the plasma contained the virus in greater concentration. Clear serum, obtained by centrifugalizing coagulated blood, no longer contained active virus. A similar result with serum was recorded by the British Commission.[19] It seems, therefore, that the virus is either enmeshed in the fibrin network of the blood clot, or is destroyed by some substance set free during clotting. The incubation period in patients inoculated with citrated blood after standing outside of the body for two or three hours, was longer than in those patients that were inoculated immediately.

In connection with the problem of immunity in trench fever it is interesting to note that the injection of blood obtained from patients on the first to the fourth days of the disease resulted in positive

17. McNee, J. W., Brunt, A., and Renshaw, E. H., loc. cit.

18. Trench Fever, Report of Commission of American Red Cross Committee, Oxford Press, London, 1918.

19. Trench Fever, W. Byam and Others: Report of British War Office Trench Fever Investigation Committee, Oxford Press, London, 1919.

infections with an incubation period of from five to seven days; while in those that were inoculated with blood obtained on the sixth or seventh day, the incubation period was from thirteen to twenty days. Furthermore, a susceptible subject injected with blood from a patient during an active relapse on the eighty-second day, did not contract trench fever. Later experiments make it reasonably certain that this blood contained virus. This evidence points to the development of immune bodies in the serum of patients as the disease progresses; such immunity explains to a certain extent the mechanism of recovery.

Our attempts to pass the virus in the plasma through a Berkefeld filter met with failure, as did the filtration experiments of McNee and his co-workers. One patient, who was inoculated with the filtrate of crushed and ground infectious erythrocytes, developed symptoms and signs of the disease from the eighth to the eleventh day, but no fever until the fiftieth day after inoculation. While the results in this single experiment were suggestive, more conclusive evidence of the filterability of the virus was not forthcoming until later, and hence will not be discussed until other evidence of the nature of the infectious agent is presented.

In none of our experiments was the virus demonstrable in the feces of trench fever patients; on the other hand, it was occasionally present in the mixed sputum and saliva. In contrast with these findings, the frequency with which the urine of trench fever patients was infectious was noteworthy. All of five subjects inoculated with unfiltered urine sediment developed the disease, although one patient was inoculated three times before positive results were obtained. The material for inoculation was prepared by centrifugalizing urine, drying the sediment to a gummy mass, and keeping it at room temperature. The combined sediment collected on different days from several patients was used in all of the experiments. Here again, the inoculation was effected by applying the material to lightly scarified skin. This series of experiments demonstrated somewhat the resistant nature of the virus, in that the high salt concentration that resulted from evaporation of urine, was sufficient to kill most bacteria and spirochetes. There is, however, some evidence that this manipulation did decrease the virulence of the infectious material, for in four of five patients inoculated with urine sediment, the incubation period was two weeks or more. Another explanation for this longer incubation period is that the virus may have been present in the urine in not so high concentration as in the blood. In framing measures for the prevention of trench fever, these experiments indicate the necessity of considering the urine and sputum as possible, if not the chief, sources of infection.

While the foregoing experiments were an important part of our work in that they prove beyond doubt the essential nature of trench fever, and provided known sources of infection for the elucidation of other problems, they were only contributory to the main object of our commission— namely, the determination of the rôle of insects in the transmission of the disease. From the beginning it was evident that military operations might interfere with the continuation of the work. The experiments were, therefore, planned to give a positive answer in the shortest time.

All of the lice used were reared from eggs and fed on normal subjects. Altogether eleven different people served to feed these normal lice, without developing the disease. Similar findings of the British Commission should serve to quiet the contention that the symptoms of trench fever may be produced by the action of normal lice.

In order to infect the lice, they were allowed to feed on trench fever patients by means of the box method. Between feedings they were kept at about 30 C. in entomologic boxes prepared from ordinary cardboard pill boxes, and were fed two or three times a day by placing the open side of the box upon the arm of the subject for thirty minutes. After several infecting feeds, they were transferred to specially prepared cells and placed on the normal subject. These cells were designed so that the lice might live under as normal conditions as it was possible to reproduce artificially. A piece of flannel shirting was placed inside of a larger piece of calico, which was then fastened to the arm of the subject by means of adhesive tape; the arm was finally covered with cotton and enclosed in a sleeve that was fastened to the skin at the top and bottom. In this form of container the insects could feed, breed, live and die, in almost the same manner as when they infest the clothing of soldiers. The only limitation of their normal activities was that they could not migrate to other portions of the body or to other persons. It was difficult for the volunteer to scratch the skin through the several thicknesses of cloth and cotton, so that at times when the cell was removed for inspection he was allowed or encouraged to scratch. In some instances, however, there were no lesions of the skin other than those produced by the stabbers of the lice. Among twenty-three subjects who harbored infectious lice in this manner, eighteen, or 78 per cent., developed trench fever. Two others, in whom a special effort was made to prevent any skin lesion, except that resulting from the bite of the lice, also developed the disease after an incubation period of four and five weeks, respectively. In these two experiments the lice never came into direct contact with the skin of the subject, but were allowed to feed by biting through the meshes of the chiffon cover of the box in which they were kept; in the intervals between feeds the boxes of lice were put in the incubator. In the

large majority of our experiments, therefore, infectious lice living under natural or artificial conditions were able to transmit the disease to susceptible subjects. In some instances the lice were on the subject for as short a time as three days; in others for as long as thirty days. In some experiments, after the infecting feeds, the lice were transferred to successive subjects in order to eliminate possible mechanical transference of the virus. The incubation periods varied between fourteen and thirty-eight days, with an average of about twenty-one days. This long incubation period should be kept in mind in connection with the scarification experiments discussed later.

The British commission [19] was less successful in transmiting the infection by the bites of infected lice. In a total of eight experiments only two subjects developed the disease. In all of these trials, however, the lice were fed entirely by the box method, as in two of our experiments mentioned above. The difference in the method employed by the two commissions explains, no doubt, the difference in their results. The failure of the workers in London to transmit the disease by the bites alone of infected lice, led them to study the effect of applying the excreta of such lice to scarified skin. This resulted in positive infections in the large majority of their experiments. This fortunate outcome opened up a fruitful field which was explored by them with brilliant results. In demonstrating this form of inoculation they developed a method that permitted the study of the evolution of the virus in both lice and patients.

It was shown that the excrement of practically all lice that have bitten trench fever patients is infectious when applied in suitable quantities to the skin of normal individuals, either by scarification or subcutaneous injection. Volunteers could also be infected by introducing the material into the conjunctival sac, but not by insufflation into the nose or by ingestion with the food. The incubation period in the majority of the patients infected by cutaneous scarification was from seven to nine days; that from conjunctival inoculation was about twice as long.

It was established that a certain interval must elapse between the infecting feed and the excretion of actual virus by the lice. In one series of experiments when the insects were fed on a patient with trench fever on the second day of his disease, this interval was five days; in another, when the infecting feed was obtained from a patient on the seventy-ninth day of his disease, the interval was twelve days. An observation of even as great interest was the length of the incubation period in the volunteers infected with excreta passed by lice on different days after the infecting feed. For instance, the incubation period in the patients infected with excrement passed on the fifth and seventh days after the infecting meal was sixteen and thirteen days,

respectively; while in the patients infected with excrement passed from the ninth to the twelfth days, it was from seven to nine days. This evidence points to one of two hypotheses: either the virus of trench fever goes through a developmental cycle in the body of the louse, or it is taken into the body of the insects in extremely minute quantities, and there must undergo an increase before it can be excreted in sufficient quantities to infect man. The fact that within certain limits the incubation period is shortened by increasing the amount of virus most easily explains why the first virus passed by the lice is less actively infectious than that passed after the ninth day. The minute quantity of the virus that may induce an attack of the disease is shown by the fact that 0.1 mg. of excrement injected subcutaneously was infectious, while 0.05 mg. was not. The proof that after a lot of lice have been infected they continue to pass the virus during the remainder of their lives also supports the hypothesis that the virus simply increases in the body of the parasites. It was further demonstrated that a single louse may pass active virus as late as thirty-two days after it has fed on a trench fever patient.

The British commission also turned its attention to the length of time during which a trench fever patient is capable of infecting lice — in other words, as to how long the virus is circulating in the blood. It is evident that in a disease such as trench fever, in which some patients show evidence of active infection for only two days and others exhibit symptoms for two years, it would be a tremendous, if not impossible, undertaking to determine when every patient is no longer infectious. Both commissions have shown that the virus is circulating in the blood of practically all patients during the first few weeks. Byam[20] and his co-workers demonstrated that lice may abstract the virus from the blood of patients showing evidence of chronic infection as late as the three hundredth and the four hundred and forty-third day after the onset of the disease. Lice were also infected by patients during periods of intermission from active symptoms in earlier stages; these subjects usually had relapses later. Two of our patients, on the other hand, failed to infect lice that were allowed to feed on them about the hundredth day after the onset of fever. It seems that when a patient has recovered completely he is no longer a source of danger. It is difficult, however, to determine when this time has arrived, for many patients after long periods of freedom from symptoms have late relapses. It is probable that such carriers of the virus, among infested troops often served to spread the disease throughout the armies.

20. Byam, W., and Lloyd, L.: Proc. Roy. Soc. Med. **13**:19, 1919.

Both commissions also showed that the virus is not transmitted to the offspring of infected lice through the eggs. The British commission demonstrated that pediculus capitis can transmit the infectious agent through the excreta in the same manner as does the pediculus corporis. Bed bugs, on the other hand, did not transmit the disease. Although no experiments are recorded on the transmission of the virus by other blood-sucking insects, it seems that the chief offender in the armies was the body louse.

We are now in a position to inquire into the nature of the infecting agent of trench fever. It is found in three different mediums: (1) Blood of patients; (2) urine of patients; (3) the excrement of lice that have fed on trench fever patients. Thus a variety of possibilities present themselves for consideration.

The early demonstration that the blood was infectious led many workers to search microscopically for the offending micro-organism, with widely divergent results. McNee and his collaborators were unable to find anything in blood films that could be definitely established as a micro-organism. They were also unable to infect patients with the Berkefeld filtrate of infectious blood. Our own investigations as to the filterability of the virus in the plasma also yielded negative results. On the other hand, one experiment with the filtrate of crushed, washed erythrocytes, known to be infectious, suggested that the negative results with filtrates of plasma containing virus might have been due to the blocking of the pores of the filter with the large colloid particles of globulin and albumin.

In this experiment the patient presented an atypical picture of trench fever, in that he had such symptoms as pain and tenderness in the usual locations, and an enlarged spleen from the second to the eighth week after inoculation, but no definite fever until the fiftieth day. Then, after a short bout of fever, accompanied by an increase of symptoms, the spleen diminished in size, and all of the symptoms of the preceding six weeks disappeared entirely. No other explanation for the peculiar clinical picture could be advanced except that a very small amount of the virus had passed through the filter, which had not been clogged with the plasma, because this substance had been removed in the washing of the erythrocytes.

After the demonstration of the infectivity of the urine of patients, and of the excrement of infected lice, it seemed advisable to repeat the filtration experiments with these substances, for in them there was probably the maximum quantity of virus with the minimum of admixed colloids. Two sets of experiments were, therefore, performed: The dried urine sediment collected from several patients was pooled and divided into two portions. One, without further treatment, was applied to the scarified skin of two volunteers in order to prove that the

material under consideration was infectious; the other was suspended in physiologic sodium chlorid solution and passed through an unglazed porcelain filter (Chamberland L) which held back *B. typhosus*. Two volunteers were injected intravenously with this filtrate. The controls, inoculated with the unfiltered sediment, developed mild types of trench fever, after incubation periods of fifteen and sixteen days, respectively. One of them suffered relapses; the other did not. The mildness of the symptoms induced in these controls indicates that the virus in this particular set of experiments was either attenuated or present only in minute quantities. One of the volunteers, injected with the urine filtrate, did not develop sufficiently distinct symptoms to warrant a diagnosis of trench fever; the other volunteer, inoculated with the same filtrate, developed trench fever after an incubation period of twenty-one days. In order to confirm the diagnosis, however, lice were allowed to feed on him from the fourth to the seventeenth days, and with their excrement another volunteer was inoculated by cutaneous scarification. He developed absolutely characteristic trench fever after an incubation period of nine days.

The last series of filtration experiments was carried out with the virus contained in the excrement of lice that had fed upon trench fever patients. One and one-half grams of this material was collected and divided into two portions. With one of them four volunteers were inoculated, all of whom developed trench fever after periods ranging from seven to ten days. The other portion was suspended in physiologic sodium chlorid solution so that the final strength of the suspension was 2 per cent. It was then passed through a Chamberland filter that held back *B. typhosus*. It is calculated that under the pressure conditions (760 mm. Hg) this filter would hold back any organism larger than that of pleuropneumonia. Three volunteers were inoculated intravenously with this filtrate. One remained free from symptoms. The second, after a period of five days, developed a low grade septic type of fever lasting seven or eight weeks, during the latter half of which time the pulse rate was much elevated; the spleen was intermittently palpable from the tenth to the thirty-fourth day; pain and tenderness, except headache, however, were never distinct features. In connection with this case, it may be recalled that Byam has demonstrated by inoculation experiments that a patient may have trench fever with an afebrile course throughout the entire period of observation. No other condition could be found in our patient to explain the peculiar clinical picture. The third of the volunteers, inoculated with filtrate of saline suspension of excrement, after an incubation period of twenty-one days, had an attack of trench fever with two relapses. During the first bout of fever there was an accompanying bronchitis;

but nothing except the occurrence of trench fever could explain the relapses with typical enlarged spleen, successive crops of macules, and characteristic pain and tenderness.

It seems definitely established, therefore, that the infectious agent, during at least one stage of its development, can be passed through a porcelain filter if the pores of the filter are not blocked with admixed protein. These experiments have been described in detail because the negative filtration experiments of other workers have cast a certain amount of doubt on the validity of our results. The failure of McNee, Brunt and Renshaw is easily explained. The only other details of experiments in reference to the filterability of the virus are a set of five reported by Arkwright.[21] Infected lice excrement was suspended in normal saline and subjected to filtration through either Berkefeld or Chamberland filters at different pressures. In two experiments in which the pressure was between 300 and 400 mm. of Hg, the injection of the filtrate was followed by entirely negative results; in a third, in which the pressure was between 200 and 300 mm. of Hg, the injection of the filtrate into a susceptible subject was followed in eight days by fever and abdominal pain, the causation of which was in doubt. In these three experiments the filter held back *B. prodigiosus*. In two other trials in which the pressure was between 600 and 740 mm. of Hg, and in which the filter allowed *B. prodigiosus* to pass, the injection of the filtrate was followed in one subject by typical relapsing trench fever, and in a second by no unusual symptoms at all. It is of interest to note that in the last two experiments the filtrate was collected from the same material during two successive periods. The advantage of having several subjects with which to test a given filtrate is well illustrated. A similar demonstration was afforded by our filtration experiments.

In connection with the filterability of the virus of trench fever, it may be recalled that a similar divergence in results has existed in the demonstration of the filterability of several of the filter passing viruses. Many experiments were made before it was established definitely that the virus of smallpox and vaccinia was filterable. Ricketts[22] was unable to filter the micro-organism shown by him to be contained in the blood of patients suffering from typhus fever. Both Nicolle[23] and Prowazek,[24] on the other hand, have demonstrated that the typhus fever virus, under proper conditions, will pass through a Berkefeld filter. In order to demonstrate the filterability of many unknown

21. Arkwright, J. A.: Brit. M. J. **2**:233, 1919.

22. Ricketts, H. T., and Wilder, R. M.: J. A. M. A. **54**:463 (Feb. 5) 1910.

23. Nicolle, C., Conor, H., and Conseil, E.: Compt. rend Acad. Sc. **151**:685 1910.

24. Von Prowazek, S.: Beitr. z. klin. d. Infectionskrank. u. z. Immunitätsfsch. **4**:5, 1915.

viruses suitable conditions must be fulfilled, and these conditions may differ with different micro-organisms. On the other hand, filterability does not mean that the micro-organism is necessarily "ultramicroscopic" during all the phases of its development. For some years the virus of yellow fever was thought to be ultramicroscopic because of the ease with which it would pass through an earthenware filter; but Noguchi [25] has lately established the spirochetal nature of the micro-organism.

Other biologic characters, moreover, place the etiologic agent of trench fever in close relationship with the group of filter-passing viruses. Mention has already been made of the manner in which the virus in infectious urine resists the concentration of salts resulting from desiccation. Byam and his co-workers have demonstrated that the virus in the excrement of lice retains its activity for at least one hundred and twenty days, even though it is exposed to the ordinary laboratory temperature and humidity, and to sunlight They [26] have also shown that it is not killed by several weeks' exposure to 50 per cent. glycerin. In their hands it resisted dry heat of 80.5 C. for twenty minutes, but was killed by exposure to 100 C. dry heat for a similar period. When moist heat was applied, it was killed by twenty minutes' exposure at 60 C. In our experiments the virus in infected louse excrement resisted 60 C. moist heat for one-half hour, but was killed after exposure to 70 C. moist heat for a similar period. The discrepancy can probably be explained by the fact that only one series of tests was carried out by each commission; no doubt heat resistance experiments would more nearly correspond, if several series were performed. The important lesson to be drawn from both experiments is that higher degrees of heat are necessary to disinfect the excreta than are required to free clothing from lice and viable eggs.

The low thermal death point of the virus demonstrates that the other resisting qualities of the micro-organism are not due to ordinary bacterial spores. The peculiar behavior of the trench fever virus in the presence of various physical and chemical agents practically rules out the possibility that it belongs to the spirochete group.

Aside from some unsubstantiated claims that a spirochete is the etiologic agent in trench fever, the most suggestive finding, from the morphologic point of view, is that of the so-called Rickettsia bodies. These bodies were first described by Ricketts [27] in the blood of patients suffering from Rocky Mountain spotted fever and in the bodies of the ticks that transmit this disease. A short time later similar bodies were observed by Ricketts and Wilder [28] in the study of typhus fever.

25. Noguchi, H.: J. Exper. M. **30**:13, 1919.
26. Personal communication of Dr. Byam to Dr. Harold Amoss.
27. Ricketts, H. T.: J. A. M. A. **52**:379, 1910.
28. Ricketts, H. T., and Wilder, R. M.: J. A. M. A. **54**:1373 (April 22) 1910.

These findings in spotted fever have been amply confirmed by Wolbach.[29] In typhus, in addition, Prowazek,[30] da Rocha-Lima,[31] and many other observers have shown that lice which have fed on patients with this disease pass large numbers of the bodies in their excreta, and also harbor many of them in the epithelial cells of the intestinal mucosa.

Morphologically, they are small bodies that vary in size from 0.3 to 0.5 by 1.5 microns. In shape, they present various outlines: cocci, diplococci and short bacilli. In the diplococcoid form the two bodies are often joined by a faintly staining substance so that dumbbell or figure 8 forms are seen. Observed under the dark field microscope, these forms have a tumbling motion, but possess no distinct motility of their own. They stain readily in films with either Giemsa or concentrated gentian violet; they are gram-negative, and not acid-fast. With Giemsa stain they take a red violet color of much the same shade as that of the nucleus of a polymorphonuclear leukocyte. Arkwright [32] states that he can distinguish the Rickettsia in lice that have fed on trench fever patients from those that have fed on typhus fever patients by the following characteristics: In trench fever fed lice the bodies are more purplish and smaller; in typhus fed lice they are larger and redder. In blood they are best demonstrated in thick drop preparations from which, after drying, the hemoglobin has been removed by distilled water or acid alcohol. Because of their small size and small numbers in the circulating blood, it is often necessary to make prolonged examination of blood films, in order to demonstrate them. They are much more easily found in the bodies of the insect vectors of these diseases. Attempts to cultivate the pathogenic forms on artificial media have resulted in failures; but both Nöller [33] and Jungmann [34] report that they have succeeded in cultivating on dextrose serum agar the Rickettsia bodies found in sheep ticks. The latter observer has shown that this species, the Rickettsia melophagi, is simply a parasite of the tick and does not produce any disease in the sheep harboring the insects. Films made from the cultures of Rickettsia melophagi show all of the forms that are seen in the excrement and the bodies of lice, and in the blood of patients.

Early in their studies various German observers described small micro-organisms that resembled the Rickettsia bodies of typhus fever in the blood of patients suffering from trench fever. This finding, combined with the supposed similarity in the mode of spread of the

29. Wolbach, S. B.: J. Med. Res. **34**:121, 1916.
30. Von Prowazek, S.: loc. cit.
31. da Rocha-Lima H.: München. med. Wchnschr. **64**: 1917.
32. Arkwright, J. A.: Proc. Roy. Soc. Med. **13**:23, 1919.
33. Nöller: Berl. klin. Wchnschr. **54**:346, 1917.
34. Jungmann, P.: (Monograph) Das Wolhysische Fieber, Berlin, 1919.

two diseases led Töpfer,[35] Jungmann and Kuczynski,[36] and da Rocha-Lima [37] to search for these bodies in the excrement and bodies of lice that had fed on patients with Wolhynian fever. Their demonstration of Rickettsia bodies in the intestinal mucosa and excrement of these lice was the chief support for their hypothesis that lice were the insect vectors of this disease. They reported that these bodies could not be found in lice until the lapse of at least five days after the insects had fed on a patient. This time corresponded so closely with the period between relapses in patients with spiky periodic fever that the German observers felt this fact furnished a further support to the hypothesis of the etiologic relationship of these bodies. Jungmann states that he was able to find them in the blood of patients with the spiky type of relapses only at the time of the relapses; on the other hand he found them in the blood of patients with continuous or typhoid type of pyrexia at any time during their fever. In spite of the attractiveness of this evidence as to the etiologic rôle of Rickettsia, it does not correspond with the findings of the British commission as to the infectivity of patients for lice. In the experiments of the last named observers, lice could be infected equally well by feeding on patients during the febrile and afebrile periods. Jungmann's observations, therefore, merely indicate a correspondence between the demonstrable presence of Rickettsia bodies in the blood and the occurrence of fever.

Jungmann and Kuczynski [38] claim that they were able to find these bipolar bodies in the blood of mice that had been inoculated with the blood of patients or with the excrement of lice that had fed on patients. Da Rocha-Lima,[39] on the contrary, was unable to infect mice, but reported that he produced the typical disease in seven out of forty-four guinea-pigs inoculated with blood, urine or lice from trench fever patients. He was, however, unable to pass the infection on to a second generation of the animals. In a series of experiments in which he allowed normal lice to bite seventy trench fever patients, 72 per cent. of the insects showed Richettsia bodies; on the other hand, 20 per cent. of the lice that had fed on patients who were supposed not to have had trench fever also showed the bodies. He explained these findings on the assumption that normal lice might be infected with a non-pathogenic type of micro-organism that he called Rickettsia pediculi. Probably a better explanation is that the patients were suffering from atypical trench fever or that some of them had a trench fever complicating the disease for which they were admitted to the hospital.

35. Töpfer, H.: München. med. Wchnschr. **63**:1495, 1916.
36. Jungmann, P., and Kuczynski, M. H.: Berl. klin. Wchnschr. **53**:323, 1916.
37. da Rocha-Lima, H.: Berl. klin. Wchnschr. **53**:567, 1916.
38. Jungmann, P., and Kuczynski, M. H.: loc. cit.
39. da Rocha-Lima, H.: Loc. cit.

Jungmann,[40] in contradistinction to da Rocha-Lima, states that he has never found Rickettsia bodies in lice that have not fed on either trench fever or typhus fever patients. Both of these observers claim that the interval between an infecting feed and the time that the Rickettsia bodies appear in the insects is about five days for trench fever and from nine to twelve days for typhus fever.

The British commission has confirmed with certain exceptions the observation of the German authors. Arkwright, Bacot and Duncan,[41] who carried out this portion of the work, had the advantage of working with a pedigreed stock of lice, as well as with experimentally produced cases of the disease from which to infect the insects. Finally, they were able to compare the appearance of the Rickettsia bodies with the infectivity of the lice for normal subjects. They [42] have lately reported that they were able to find Rickettsia bodies in all of 108 boxes of lice that had fed several times on sixty-four trench fever patients. In only one out of many lots of the insects fed only on normal persons, were forms found that suggest trench fever Rickettsia bodies. In their experiments, a volunteer inoculated with a single louse that contained the Rickettsia bodies contracted trench fever, while another subject inoculated with a single louse from the same box, but free from Rickettsia bodies, remained well. There was also a remarkable correspondence between the appearance of Rickettsia bodies in the excrement of lice after the infecting feed and the virus content of the same excrement when inoculated into susceptible volunteers. The interval between the infecting feed and the appearance of the bodies varied from five to twelve days, with an average of from seven to ten days. This time is longer than that reported by the Germans, but corresponds closely with the average incubation period in patients inoculated with the excreta of infected lice. Lice that were fed on patients with experimentally produced trench fever during the first day only did not subsequently show Rickettsia bodies; although lice fed later on the same patients did show them. In this connection it is of interest to note that the only lice that were usually not infectious in our original experiments were those that were fed on patients during the last two days of the incubation period and during the first two or three days of the fever. Blood from these same patients, however, contained virus, as demonstrated by intravenous inoculation. In all types of experiments, with one exception, therefore, there is a striking parallelism between the infectivity of the insect vectors and the appearance of Rickettsia bodies. This exception was reported by Arkwright

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40. Jungmann, P.: (Monograph), loc. cit.
41. Arkwright, J. A., Bacot, A., and Duncan, F. M.: J. Hygiene **18**:76, 1919.
42. Arkwright, J. A.: Proc. Roy. Soc. Med. **13**:23, 1919.

and Byam [43] and is as follows: Two lots of lice were allowed to feed on a trench fever patient; one lot was kept at a temperature of from 27 to 30 C. and developed Rickettsia bodies; the other lot was kept at 17 C. and did not develop them. The excrement from both lots of lice proved to be infectious by inoculation into normal volunteers.

While it is difficult not to believe that there is a causal relationship between the virus of trench fever and the Rickettsia bodies, it will be difficult to establish definitely such a relationship until it is possible to obtain pure cultures of the bodies and with them to reproduce the disease. In this connection it must be recalled that the relation of Rickettsia bodies to other micro-organisms has not been established. They may be specific micro-organisms; they may be a granular stage through which some other micro-organism is passing; or, finally, they may be cell inclusions, the result of the action of some invisible virus on the cell protoplasm, and thus resemble the Guarnieri bodies in vaccinia, the Negri bodies of rabies, the molluscum bodies in molluscum contagiosum and the cell inclusions in trachoma.

In our efforts to determine the pathogenesis and histologic changes in this disease, we are handicapped by inadequate knowledge as to the nature of the virus and by a total lack of necropsies. The non-fatal character of the disease has made it impossible to examine thoroughly all of the tissues of the body for the site of attack of the virus. In addition, the failure to reproduce the typical disease in lower animals has forced us to resort entirely to the study of the various clinical manifestations in man, in order to arrive at some understanding of the nature of the infection.

In the two other well known diseases that are associated with the appearance of Rickettsia bodies in the insect vectors of the virus, it has been established that the chief structures showing definite histologic changes are the small blood vessels. Wolbach [44] has shown that the reaction in Rocky Mountain spotted fever is "an endangitis, characterized by endothelial cell proliferation, local necrosis of endothelium and smooth muscle, and thrombosis. Perivascular accumulations of large mononuclear cells are of common occurrence." The lesions are limited practically to the skin and genitalia. Fraenkel [45] has demonstrated that the essential lesion in typhus fever is the same; but in the latter disease the vessels of the viscera are also involved. Schminke [46] has compared the histologic changes in the exanthems of trench fever and of typhus, and shown that in the hyperemic and edematous corium of trench fever macule there is a perivascular lymphocytic infiltration mixed

43. Report of British Trench Fever Commission, loc. cit.
44. Wolbach, S. B.: J. Med. Res. **37**:499, 1918.
45. Fraenkel, E.: München. med. Wchnschr. **62**:805, 1915.
46. Schminke, A.: München. med. Wchnschr. **64**:961, 1917.

with some polymorphonuclear leukocytes. The endothelium and vessel wall necrosis and hyaline thrombosis, found in typhus fever lesions, was entirely absent. This probably explains why the trench fever exanthem is not petechial. In typhus fever the intensely toxic nature of the virus leads to an actual death of the cells and often of the patient; while in trench fever the less toxic virus does not lead to a destruction of either cell or host. A similar action on the body of the insect vector of the two diseases has been found. Both the English and German observers have noted that lice that have bitten trench fever patients live their normal number of weeks; on the other hand, Jungmann and da Rocha-Lima call attention to the fact that the life of lice is shortened by feeding on typhus fever subjects.

Clinically, the main tissues that seem to be involved in trench fever, aside from the skin, are the hematopoietic organs and the nervous system. The polymorphonucleosis during the febrile paroxysms, followed by an increase in the mononuclear elements of the blood, and the peculiar enlargement of the spleen all indicate that the virus has a marked effect upon the blood forming and blood destroying organs. There has been much discussion as to the cause of the peculiar pain and tenderness in patients with this disease. These symptoms are not accompanied by other signs of local inflammation of the periosteum, muscles or tendons, such as swelling, redness or edema. The description of the pains given by many patients resembles the pains that occur in the early stages of tabes dorsalis. Byam,[47] Carmalt Jones,[48] and others, have called attention to the peculiar distribution of cutaneous hyperesthesia in the areas supplied by the eighth cervical, first and seventh dorsal, and all the lumbar segments of the cord, during the active stages of the disease. Sundell [49] has observed that later there is a distinct blunting of the cutaneous sensibility over similar areas. These sensory disturbances, coupled with the increase in tendon, cutaneous and pilomotor reflexes, all point to some abnormal condition of the sensory tracts, probably in the region of the dorsal roots. The condition of "disordered action of the heart," a late complication in certain patients, can best be explained on the basis of a disturbance of the autonomic nervous control of the cardiac action. In patients suffering from this peculiar group of symptoms or from neurasthenia following an attack of acute trench fever, there is usually evidence that the disease is still active in a chronic form.

The many forms of fever that have resulted from the artificial inoculation of different individuals with the same strain of virus have

47. Byam, W., Dimond, L., Sorapure, V. E., and Wilson, R. M.: J. R.A.M.C. **29**:560, 1917
48. Carmalt Jones, D. W.: Lancet **2**:443, 1918.
49. Sundell, C. E.: Lancet **2**:538, 1918.

demonstrated that the various clinical types of the disease are not due to different varieties of the micro-organism, as is the case in malaria. The spiky type of paroxysm, requiring but a single day for its completion, can best be explained on the assumption that the virus requires a certain time for its complete development in the tissues of the patient; when that period is complete, the micro-organisms or a toxin that they develop as a result of their activity, flood the patient, and give rise to the explosive picture. If, on the other hand, the micro-organisms are of different age, either as a result of multiple inoculation, or because of a mixture of virus of different ages, they will attain their maximum growth in the patient's body at different times, and produce a septicemic or typhoid type of fever.

Recovery from the disease is evidently due to the development of an immunity on the part of the patient. The time required for the development of this immunity varies within wide limits. No doubt some individuals possess a complete immunity to the infection. In others there is a partial immunity, so that the introduction of the virus into their bodies results in abortive or larval types of the disease. In the majority of patients, complete immunity develops only after repeated flooding of the body with the virus; and, on the average, requires from three to six weeks for its production. Even then it may be only partial—sufficient to hold in abeyance all symptoms until the patient is subjected to some general depressing influence, when a relapse occurs. Among our volunteers we had a number of examples of such relapses after prolonged periods of absence of fever and symptoms; and lately I have seen in a physician a relapse that occurred twenty-six months after the original attack in Flanders. Such prolonged periods of freedom from symptoms with subsequent relapses remind one of similar conditions in malaria and syphilis.

In still another group of patients months or years are required for complete immunity to develop. This group comprises from 5 to 10 per cent. of all of the patients afflicted with the disease. In them the manifestations assume a subacute or chronic form; the patients are never entirely free from symptoms; occasional low grade fever is found. The condition is variously described by the terms myalgia, neuralgia, neurasthenia, disordered action of the heart, or trench fever cachexia. Byam and his associates have shown that at least some of these sufferers are carrying the virus in their blood as late as from three to four hundred days after onset of fever.

The immunity that develops with recovery is of relatively short duration. The British commission showed that reinfection was possible on the one hundred and thirty-second and one hundred and ninety-

eighth days after the onset; Werner [50] reinfected himself six months after his first attack. On the other hand, the British commission found it impossible to reinfect some patients at periods varying from sixty-two to 182 days after the onset. Irregularity in the duration of immunity seems to be as much a feature of the disease as irregularity in the time of development of immunity and as irregularity in most of the symptoms.

The practical application of all the knowledge that has been gained by much effort is that eradication of the louse in infected bodies of men is followed by a cessation of the disease. The discussion that has arisen as to whether the chief mode of human infection is through the bite of the insects or results from introduction of louse excretion into excoriated skin is more academic than practical. The method of inoculation by applying louse excrement to scarified skin has resulted in much useful knowledge concerning both human and insect carriers of the disease. It has been the experience of many observers that the wholesale application of measures against louse infestation has been followed by a diminution in the incidence of the disease. This was strikingly brought out in the experience in the Third Army of the American Expeditionary Forces.[51] The experience in the Presbyterian Base Hospital Unit [52] of this city showed that infected and infested clothing and equipment may be handled with impunity, provided the people handling such material are protected against lice. The chance for contracting infection from patients was as great, or greater, after May, 1918, as before, but the simple institution of effective measures against the possibility of . becoming infested with lice from the patients, resulted in practical freedom from new infections among nurses and orderlies.

SUMMARY

During the recent war a disease, hitherto unrecognized as a clinical entity, was widespread throughout the armies on both the eastern and western fronts. Although the manifold forms of the affection make accurate statistics impossible, it is estimated that between 800,000 and 1,000,000 cases must have occurred. Before the influenza epidemic it was the most frequent single disease in several of the armies. While not fatal, it usually resulted in disability for from ten to twelve weeks, and in 10 per cent. of the cases was the cause of invalidism for many months. In such instances the infection is active in a chronic form. The many clinical forms of the disease are apparently not due to the

50. Werner, H., and Benzler, J.: München. med. Wchnschr. **64**:695, 1917.

51. Swift, Homer F.: J. A. M. A. **73**:807 (Sept. 13) 1919.

52. Prevention of Trench Fever Among Hospital Personnel, Mil. Surgeon **44**:370, 1919.

action of different types of micro-organism, but to single or multiple infections with a single type of organism. The intensity and duration of an attack seem to depend on the relation between the infectivity of the virus and the immunity in the patient.

It has been demonstrated that the disease is not a modified form of enteric or typhus fever, but that it is due to a specific infectious agent. This etiologic agent behaves in the presence of various physical and chemical environments in a manner similar to that of many of the filter passing micro-organisms. Under suitable conditions the virus of trench fever will pass through the pores of a filter that are small enough to hold back ordinary bacteria. The virus is found occasionally in the sputum of patients, often in the urine, and always in the blood at some stage. It is also found in the excrement and bodies of practically all lice that have fed several times on trench fever patients, after an interval of from five to ten days following the infecting feed. After a louse has started to excrete active virus, it continues to do so for the remainder of its life. The virus is not transmitted to the larvae of lice through the eggs. The interval elapsing between the time of the infecting feed and the first excretion of virus by lice closely corresponds with the length of the incubation period in men inoculated with a maximum dose of virus. There is a remarkable correspondence in the infectivity of louse excrement and the time of appearance of Rickettsia bodies; these bodies are also demonstrable, with difficulty, in the blood of patients during the period of pyrexia. The etiologic rôle of Rickettsia bodies, however, as well as the relation of these bodies to micro-organisms in general, remains to be established.

While men may be infected by the simple bites of infected lice, they are more surely infected by applying the excrement of such lice to scarified skin; infected lice, living under normal conditions, transmit the disease to the majority, if not to all, men harboring them. As a direct corollary, the eradication of lice is followed by an eradication of the disease.

A STUDY OF PHOSPHATE RETENTION FROM THE STANDPOINT OF BLOOD ANALYSIS *

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During the past five years our knowledge regarding the content of inorganic phosphates in blood has been advanced by the work of several investigators: Taylor and Miller,[1] Greenwald,[2] Marriott and Howland,[3] Feigl[4] and Bloor[5] have published the results of determinations of the inorganic phosphate content of plasma. Each investigator has worked by a different method, but, with the exception of the results obtained by Taylor and Miller, who state that the inorganic phosphate content of plasma is so small as to be negligible, the average values reported by the other workers are within the same general range.

In certain cases of nephritis, Greenwald and Marriott and Howland have reported the presence of greatly increased amounts of inorganic phosphates in plasma, the importance of which finding, in connection with both the theoretical and practical aspects of nephritic acidosis, has been pointed out by the latter workers.

More than a year ago, on the publication of Bloor's exceedingly simple method for the determination of inorganic phosphates in plasma, we began the accumulation of data on the subject with the immediate object of finding out whether a knowledge of the inorganic phosphate content of plasma might be of value in the prognosis or diagnosis of renal disease. As a preliminary to our work on nephritic conditions, it seemed necessary, in view of the relatively small number of figures to be found in the literature, to make determinations of inorganic phosphates in the plasma of patients suffering from conditions other than renal or cardiorenal. A statement of the values obtained with this class of material is contained in Table 1. In many cases the nonprotein nitrogen was also determined, and where available these figures have been included in the tabulated results.

From the results presented in Table 1 it would seem that the inorganic phosphates in serum in various pathologic conditions other than nephritis or cardiorenal disease, may vary from 1.2 to 3.1 mg. of phosphorus per hundred c.c. of plasma. Bloor's results on twenty-seven normal persons give slightly higher values, i. e., minimum 1.8 and maximum 4.3 mg.

* From the Chemical Laboratory of the Massachusetts General Hospital.
1. Taylor, A. E., and Miller, C. W.: J. Biol. Chem. **28**:205, 1914.
2. Greenwald, I.: J. Biol. Chem. **29**:21, 1915.
3. Marriott, W. McK., and Howland, J.: Arch. Int. Med. **18**:708, 1916.
4. Feigl, J.: Chem. Abstr. **11**:3316, 1917; **12**:809, 1918.
5. Bloor, W. R.: J. Biol. Chem. **36**:49, 1918.

TABLE 1.—Inorganic Phosphates in Blood

Case No.	Mg. per 100 C.c. Plasma		Diagnosis
	Inorganic Phosphates as P.	Non-protein Nitrogen	
20	1.2	40	Anemia (secondary)
10	2.0	..	Arthritis (chronic)
30	2.0	38	Arthritis (chronic)
40	3.1	52	Arthritis (chronic)
88	2.1	40	Arthritis (chronic)
70	1.8	44	Arthritis (acute)
73	2.7	37	Arthritis (acute)
150	2.2	44	Arthritis (acute)
164	2.4	31	Arthritis (acute)
177	2.3	41	Arthritis (acute)
180	2.5	34	Arthritis (acute)
194	2.6	30	Arthritis (acute)
198	2.4	36	Arthritis (acute)
211	2.3	40	Arthritis (acute)
232	2.0	34	Arthritis (acute)
253	3.2	37	Arthritis (acute)
25	1.8	..	Diabetes
32	1.4	..	Diabetes
34	1.9	..	Diabetes
38	2.0	..	Diabetes
43	1.6	..	Diabetes
44	2.6	32	Diabetes
54	1.8	42	Diabetes
62	1.7	30	Diabetes
74	2.6	35	Diabetes
144	2.6	..	Diabetes
203	2.8	42	Diabetes
24	1.8	30	Influenza
99	2.1	38	Influenza
42	1.6	46	Influenza
7	1.8	32	Gastric ulcer
5	1.8	42	Gastric ulcer
16	2.6	32	Gastric ulcer
143	2.3	38	Gastric ulcer
19	1.6	32	Gastric cancer
35	2.6	50	Gastric cancer
97	2.1	30	Gastric carcinoma
189	2.4	47	Gastric carcinoma
190	2.7	43	Gastric carcinoma
9	1.6	..	Jaundice (catarrhal)
39	3.1	34	Jaundice (catarrhal)
79	2.2	40	Jaundice (catarrhal)
51	2.6	38	Hyperthyroidism
63	1.8	40	Hyperthyroidism
163	3.0	33	Hyperthyroidism
56	3.1	48	Syphilis (cerebrospinal)
84	2.2	35	Syphilis (cerebrospinal)
195	1.7	40	Syphilis (cerebrospinal)
220	2.7	44	Syphilis (cerebrospinal)
224	2.1	45	Syphilis (cerebrospinal)
231	3.2	33	Syphilis (cerebrospinal)
233	2.3	37	Syphilis (cerebrospinal)
234	2.8	37	Syphilis (cerebrospinal)
139	3.1	40	Pneumonia (bronchial)
144	1.8	32	Pneumonia (lobar)
145	2.3	42	Pneumonia (lobar)
157	1.5	44	Pneumonia (lobar)
206	2.9	40	Pneumonia (lobar)
138	1.3	52	Pulmonary tuberculosis
148	2.3	30	Pulmonary tuberculosis
57	1.8	..	Psoriasis
86	3.0	..	Psoriasis
141	2.0	31	Psoriasis
58	1.8	..	Chronic eczema
101	1.3	36	Chronic eczema
115	1.8	..	Chronic eczema
134	2.6	40	Chronic eczema
238	3.1	38	Chronic eczema
179	2.7	42	Chronic eczema
239	2.8	35	Herpes zoster
6	1.8	37	Torticollis
45	2.9	32	Normal pregnancy
60	1.8	68	Gangrene of leg
71	1.8	44	Gangrene of leg
200	2.0	45	Osteomalacia
38	2.1	44	Cholelithiasis
40	2.8	60	Pituitary tumor
140	2.6	57	Acute endocarditis
127	2.1	47	Lead poisoning (chronic)
233	2.2	35	Valvular disease (chronic)

The results obtained on sixty-eight cases of renal and cardiorenal disease have been collected in Table 2. These cases have been arranged according to the level of plasma phosphates, and without regard to the anatomic nature of the lesions.

From the figures collected in Table 2 it is apparent that many nephritic and cardiorenal cases sufficiently ill to enter a hospital show no retention of inorganic phosphate in their plasma. Out of the sixty-eight cases included in this tabulation, twenty four (about 35 per cent.) showed an inorganic phosphate content of plasma equal to or below the maximum obtained in the miscellaneous material examined, the results on which are shown in Table 1. In view of the fact that our cases were not selected, and that we simply made use of all material available during the period in which this study was in progress, it is, perhaps, not unjustifiable to conclude that at least 60 per cent. of the ordinary cases of nephritis with or without cardiac involvement, show a retention of inorganic phosphate in the plasma.

In Table 3 we have grouped together eleven cases of nephritis and allied conditions on which we were able to make several blood examinations during the course of the patient's stay in the hospital and to thus learn something of the changes in the level of plasma phosphate which may occur when the clinical condition of the patient is improving, and when the symptoms are increasing in severity.

An inspection of the results presented in Table 3 shows that of the eleven cases included in the group, nine patients died, while two were discharged relieved.

In all fatal cases the "premortal" rise in plasma phosphate is most striking. It will also be noted that in the two nonfatal cases the plasma phosphate, while distinctly above our maximum "normal" figure, did not, at any time, rise to an alarming height. The lack of concordance between the increased content of inorganic phosphate and the nonprotein nitrogen has been noted by Greenwald, and by Marriott and Howland; our results offer numerous confirmations of the findings of these investigators.

We wish also to call attention to the lack of any definite relation between the plasma phosphate and the alkaline reserve, a finding not without interest when viewed from the standpoint of modern theories of acid base equilibrium.

In this connection it may be of interest to state that we have had several opportunities of confirming the findings of Marriott and Howland regarding the entire lack of effect produced by sodium bicarbonate medication on the level of plasma phosphate.

In conclusion, it may be said that, as far as one can judge from the limited data available, the determination of the inorganic phosphate of the plasma gives promise of being of value in connection

TABLE 2.—Inorganic Phosphates in Plasma in Nephritis and Cardiorenal Disease

Case No.	Mg. per 100 C.c. Plasma		Alkal. Reserve Con. Value per Cent.	
	Inorganic Phosphate as P.	Non-protein Nitrogen		
14	1.9	33	..	Chronic nephritis, hypertension
147	1.9	32	..	Acute nephritis
110	1.9	36	..	Chronic nephritis, hypertension
149	2.0	38	46	Arteriosclerosis, chronic nephritis
151	2.0	40	..	Cardiorenal disease
21	2.1	..	..	Arteriosclerosis; senile heart; chronic nephritis
16	2.2	32	..	Chronic nephritis, hypertension
53	2.2	38	..	Acute nephritis
136	2.2	34	..	Cardiorenal disease
158	2.4	38	..	Subacute glomerulonephritis
255	2.4	30	51	Senile arteriosclerosis; chronic nephritis
152	2.5	46	42	Arteriosclerosis; chronic myocarditis; chronic nephritis
271	2.5	38	60	Arteriosclerosis, chronic nephritis
156	2.5	50	66	Arteriosclerosis, hypertension; chronic nephritis; diabetes
15	2.6	40	..	Arteriosclerosis; cardiorenal disease
29	2.6	60	..	Chronic interstitial nephritis
47	2.6	40	..	Mercury poisoning, acute
100	2.6	75	..	Chronic nephritis
108	2.6	47	..	Mercury poisoning, acute
117	2.7	66	..	Chronic nephritis
77	3.1	84	..	Chronic glomerulonephritis
283	3.1	66	..	Chronic nephritis, hypertension; albuminuric retinitis
165	3.1	62	..	Chronic nephritis
196	3.1	48	42	Cardiorenal disease
88	3.2	64	..	Chronic nephritis
90	3.2	41	..	Chronic nephritis
37	3.4	40	..	Mercury poisoning, acute
96	3.4	40	..	Arteriosclerosis, chronic nephritis
105	3.4	36	..	Chronic nephritis
107	3.4	37	..	Chronic nephritis
267	3.5	96	33.6	Chronic nephritis, uremia
169	3.6	36	..	Chronic nephritis, uremia
223	3.6	44	57	Cardiorenal disease
168	3.7	40	46.3	Syphilis, chronic nephritis
228	3.7	45	..	Cardiorenal disease
162	3.8	76	33.8	Subacute nephritis, bronchopneumonia, uremia
104	3.8	34	..	Chronic nephritis
235	3.9	50	30	Chronic nephritis, hypertension
174	4.0	40	..	Chronic nephritis, hypertension
72	4.0	..	..	Aortic and mitral insufficiency, chronic nephritis
109	4.1	B5	..	Chronic nephritis
208	4.4	55	52	Chronic nephritis
219	4.0	56	54	
248	4.2	55	59	Myocardial weakness, hypertension, chronic nephritis
230	4.3	32	56	Chronic nephritis
204	4.4	40	49	Cardiorenal disease, diabetes
218	4.4	40	42	
199	4.4	34	..	Chronic nephritis, amyloid kidney, uremia
269	4.4	190	..	Chronic glomerular nephritis, uremia
160	5.3	143	30	Cardiorenal disease, uremia
222	5.3	56	52	Chronic nephritis
8	5.3	55	..	Chronic nephritis
257	5.3	47	48	Chronic nephritis
226	5.3	50	46	Cardiorenal disease
161	5.6	161	30	Subacute glomerular nephritis, uremia
252	16.0	164	46	Chronic glomerular nephritis, uremia
207	6.1	47	..	Chronic nephritis
205	6.0	50	50	Chronic nephritis
209	6.0	190	37	Chronic glomerular nephritis, uremia
270	6.0	164	33	Chronic nephritis
67	6.2	36	..	Hypertension, arteriosclerosis, chronic nephritis
247	6.2	74	45	Hypertension, chronic nephritis
182	7.8	54	49.6	Chronic nephritis, hypertension
275	8.4	118	..	Chronic nephritis, hypertension
106	8.5	63	..	Chronic nephritis
154	10.3	180	..	Pyelonephritis
289	12.4	237	21	Chronic nephritis, hypertension, arteriosclerosis, uremia
290	12.4	298	..	Chronic myocarditis, chronic nephritis, uremia
284	18.0	205	..	
236	14.8	192	..	Chronic nephritis, hypertension, uremia
237	22.3	222	46	
205	28.1	50	51	Myocardial insufficiency, chronic nephritis

with progress in renal and cardiorenal disease. We have noted cases in which the nonprotein nitrogen was high, the phenolsulphonephthalein output extremely low, and the plasma phosphate but slightly increased. These patients, whatever may have been their later fate, invariably left the hospital relieved of their more serious subjective symptoms. An example of this type is Mr. M. (Table 3).

On the other hand, many, although we are not prepared to say all, fatal cases show a rapidly rising plasma phosphate.

TABLE 3.—Changes in Level of Plasma Phosphate in Nephritis
and Allied Conditions .

| Date, 1919 | Mg. per 100 C.c. Plasma | | Alkali Reserve Con. Value per Cent. | |
	Inorganic Phosphate as P.	Non-protein Nitrogen		
Jan. 18	6.0	72	....	Mr. T. Chronic glomerular nephritis, uremia. Died
Jan. 20	6.0	82		
Jan. 30	10.3	122		
Jan. 31	15.6	200	43.0	
Jan. 14	15.5	100	....	Mr. B. Hypertension, arteriosclerosis, cardiorenal disease, uremia. Died one hour after last sample of blood was taken
Jan. 16	43.7	113		
Jan. 18	43.7	180		
Jan. 28	2.0	56	....	Mr. S. Aortitis, syphilis, cardiorenal disease. Died
Jan. 30	2.0	40		
Feb. 1	2.0	40		
Feb. 5	9.1	62		
Feb. 13	3.4	68	....	Mrs. P. Mercuric chlorid poisoning. Died three days after last sample of blood was taken
Feb. 15	3.9	100		
Feb. 16	4.5	125		
Feb. 18	9.2	140		
Feb. 13	3.5	62	....	Mr. S. Aortic stenosis and regurgitation, chronic interstitial nephritis. Died
Feb. 19	3.5	65		
Feb. 27	6.5	90		
Mar. 10	2.8	105	....	Mr. B. Chronic glomerular nephritis, uremia. Died
Mar. 15	9.4	167	27.0	
Mar. 19	15.0	200	26.2	
Mar. 15	6.5	153	....	Mrs. T. Chronic glomerular nephritis, uremia. Died
Mar. 19	7.5	250	28.1	
Mar. 20	8.1	278	22.0	
April 21	4.5	143	24.2	Mr. M. O. Chronic interstitial nephritis uremia. Died. On April 26 sodium bicarbonate was administered intravenously
April 25	10.0	152	24.2	
April 26	9.8	165	15.4	
April 26	9.8	165	26.0	
April 27	10.4	163	20.1	
July 2	3.6	69	54.0	Mr. D. Chronic glomerular nephritis. Died
July 10	9.4	103		
July 15	11.6	140		
July 18	17.7	160	24.1	
July 22	18.9	208	22.4	
Sept. 3	4.3	166	....	Mr. B. Jaundice (cause unknown), emphysema, nephritis. Discharged relieved
Sept. 6	4.0	75		
Sept. 16	2.8	36		
Sept. 26	2.4	39		
Mar. 10	3.3	72	....	Mr. M. Chronic myocarditis, mitral regurgitation and stenosis, cardiac decompensation, chronic nephritis. Discharged relieved
Mar. 17	3.3	125		
Mar. 19	3.5	142		
Mar. 20	3.0	105	43.0	
Mar. 23	2.1	66	46.6	
Mar. 24	1.6	49	48.6	
Mar. 27	1.6	113		

SUMMARY

As a result of our study of the inorganic phosphate content of plasma, it has been shown that about 65 per cent. of the nephritic and cardiorenal cases, taken at random from the material found in the hospital wards, gave unmistakable evidence of phosphate retention. Fatal cases showed a rapid and progressive increase in plasma phosphate, increases of more than ten times the maximum normal value having been noted; the nonfatal cases, even though the patient was seriously ill, presented a relatively slight increase. The results obtained suggest the possible prognostic importance of the determination of inorganic phosphates in the plasma of persons suffering from nephritis and allied disorders.

A NEW ELECTRODE FOR USE IN CLINICAL ELECTROCARDIOGRAPHY *

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It has become sufficiently clear that if in taking human electro-cardiograms there is overshooting of the string, a high resistance has probably developed at the site at which the electrodes have been applied to an individual. Overshooting is, of course, undesirable because it deforms the curve. A high metallic resistance interposed in the circuit does not cause this defect. The deformity is seen either when an added resistance is introduced into the circuit or when a current passes. In the latter instance the overshooting is the greater, the greater the voltage. It has likewise become sufficiently clear, that if the resistance in the string-patient circuit is reduced below 2,000 ohms, the overshooting does not take place. It makes no difference so far as electrocardiography is concerned what is the reason of the overshooting—whether due to polarization at the electrodes or to a capacity effect in the cutaneous tissues as Pardee [1] has suggested.

TABLE 1.—RESISTANCES OBTAINED WITH VARIOUS ELECTRODES

Order of Taking Electro-cardiograms	Type of Electrode	Fig-ure	Resistance Before Salt Rub			Order of Taking Electro-cardiograms	Fig-ure	Resistance After Salt Rub		
			Lead 1 Ohms	Lead 2 Ohms	Lead 3 Ohms			Lead 1 Ohms	Lead 2 Ohms	Lead 3 Ohms
1	Plate	..	2,300	4,500	4,000	6	6	2,300	2,300	1,400
2	Lead	3	2,000	2,500	2,300	5	4	1,000	1,000	1,000
3	Immersion	..	4,000	3,000	3,400	4	5	2,500	2,500	2,000
7	German silver	..	.....	.....	.....	..	7	1,400	1,400	1,400

Provided, then, that the resistance is low, the form of electrode used is probably a matter of indifference. The electrode of choice is the one easiest to apply, easiest to keep in order, easiest and cheapest to make. At the Hospital of the Rockefeller Institute the electrode in use is made of a strip of lead foil [2] 7.5 cm. wide by 22.0 cm. long, and

1. Pardee, H. E. B.: An error in the electrocardiogram arising in the application of the electrode, Arch. Int. Med. **20**:161 (Aug.) 1917.

2. The lead foil is an alloy of lead and tin known as roentgen-ray protection foil. The gage used is B. & S. 31. It is supplied in rolls 12 inches wide. The rubber strip is cut from rubber matting 1/16 inch thick, 3 feet wide, which may be obtained from the New York Belting and Packing Company.

of a strip of rubber sheet 9.0 cm. wide by 30.0 cm. long. The two strips are fastened together about 8.0 cm. from one end by a brass screw, brass binding post and washers, in the manner shown in Figures 1 and 2. No soldering is necessary. The manner of fastening permits the repeated use of the remaining portion of the lead foil if a break takes place at the binding post. This accident after prolonged use is of course unavoidable.

In order to test and to establish the usefulness of these electrodes, electrocardiograms made with them (Figs. 3 and 4) were compared with others taken with immersion-non-polarizable electrodes (Fig. 5), with the so-called plate electrodes (Fig. 6), and with German silver

TABLE 2.—Measurements of the —

Electrodes	Figure		P₁*	P₂	P₃	Q₁	Q₂	Q₃
			Mm.	Mm.	Mm.	Mm.	Mm.	Mm.
Lead............	3	Range	1.0-1.1	1.0	0.2 - 0.4	2.75-3.1	—	—
Lead............	4		0.9-0.1	1.05-1.15	0.50- 0.62	2.4 -2.9	—	—
Immersion......	5		1.00	1.0	0.43- 0.6	2.4 -2.65	—	—
Plate..........	6		1.0 - 1.5	1.2-1.5	0.6 - 0.8	2.5 -3.0	—	—
German silver...	7		0.75- 1.2	0.9-1.0	0.8 - 0.1	2.55-2.8	—	—
Lead............	3	Observed	1.05	1.0	0.33	2.85	—	—
Lead............	4	average	0.95	1.09	0.57	2.68	—	—
Immersion......	5		1.0	1.0	0.50	2.53	—	—
Plate..........	6		1.07	1.31	0.71	2.72	—	—
German silver...	7		0.91	0.97	0.92	2.69	—	—
			Mm. %	Mm. %	Mm. %			
Lead............	3	Observed	21.51 = 107.5	21.5 = 107.5	20.13 = 100.65	Same	Same	Same
Lead............	4	standard	20.3 = 101.5	21.01 = 105.05	21.3 = 106.5	as	as	as
Immersion......	5	deflection†	20.53 = 102.65	20.59 = 102.95	20.57 = 102.85	P₁	P₃	P₂
Plate..........	6		21.08 = 105.4	21.05 = 105.25	20.43 = 102.15			
German silver...	7		20.16 = 100.8	21.08 = 105.4	21.28 = 106.4			
Lead............	3	Corrected	0.98	0.93	0.33	2.65	—	—
Lead............	4	average	0.94	1.04	0.54	2.64	—	—
Immersion......	5		0.97	0.97	0.49	2.47	—	—
Plate..........	6		1.02	1.25	0.70	2.58	—	—
German silver...	7		0.90	0.98	0.87	2.67	—	—

* $P_1 = $ P wave in Lead 1; $P_2 = $ P wave in Lead 2, etc.
† The standard deflection when 20 ohms are thrown into string circuit is 20.0 mm. If 20.0 mm. equals 100 per cent., a deviation from this height of the observed deflection may be expressed in per cent. This figure is used for correcting the observed average to 100 per cent.

electrodes (Fig. 7). The plate electrodes were fashioned after the manner of those introduced by the Cambridge Instrument Company; those of German silver after the pattern described by Williams;[3] the nonpolarizable ones in the manner which is usual when the extremities are immersed. The electrocardiograms were taken of a single individual at a single sitting in the order shown in Table 1.

After exposures noted in the first column were made (Table 1), the arms and leg of the patient were rubbed gently with warm saturated salt solution; then those recorded in the second column were taken. Taking all the electrocardiograms occupied about one hour. Slight

3. James, W. B., and Williams, H. B.: The electrocardiogram in clinical medicine, Am. J. M. Sc. **140**:408, 1910.

overshooting is seen in Figure 3 (the lead electrode before rubbing), and in Figure 5 (the immersion nonpolarizable electrode). On the whole, the resistance was highest when these two were taken. In comparing them, however, it is not the object to show the relation of resistance to the degree of overshooting, but to show the fact that the electrocardiograms, irrespective of the form of the electrodes, are closely comparable at resistances of this magnitude.[4]

That the curves are comparable is shown (Table 2) by the fact that the height of a wave in one lead, the R wave for instance in Lead 1, differs little from the other R waves in the same lead, that is to say,

— Waves in Figures 3 to 7

R_1	R_2	R_3	S_1	S_2	S_3	T_1	T_3	T_2
Mm.	Mm.	Mm.	Mm.	Mm.	Mm.	Mm.	Mm.	Mm.
18.4-19.0	9.5 -10.1	4.25-4.7	—	2.7-3.0	15.1 -15.9	1.95-2.1	1.9 -2.36	—0.65 - —0.7
17.4-18.26	8.7 - 9.13	4.25-4.5	—	1.5-2.0	13.8 -15.0	2.0 -2.3	1.85-2.15	—0.5 - —0.8
15.8-17.0	8.6 - 8.95	4.1 -4.85	—	2.2-2.65	12.7 -14.65	2.1 -2.2	1.75-2.1	—0.4 - —0.67
18.2-19.75	8.42- 8.85	3.85-4.25	—	1.2-2.0	13.75-15.4	2.5 -2.7	1.85-2.35	—0.6 - —0.87
17.7-19.2	8.55- 8.9	3.95-4.2	—	1.0-1.17	13.82-15.27	2.25-2.72	2.1 -2.35	—0.35 - —0.45
18.7	9.90	4.46	—	2.87	15.55	2.02	2.08	—0.68
17.68	8.97	4.44	—	1.67	14.64	2.13	2.00	—0.60
16.45	8.77	4.44	—	2.43	13.73	2.12	1.98	—0.50
19.04	8.70	4.03	—	1.61	14.88	2.56	2.03	—0.72
18.75	8.76	4.11	—	1.06	14.66	2.51	2.22	—0.38
Same as P_1	Same as P_2	Same as P_3	Same as P_1	Same as P_2	Same as P_3	Same as P_1	Same as P_3	Same as P_2
17.39	9.21	4.43	—	2.67	15.45	1.88	1.94	—0.68
17.43	8.55	4.17	—	1.59	13.75	2.15	1.90	—0.56
16.03	8.52	4.32	—	2.37	13.36	2.07	1.93	—0.49
18.06	8.27	3.95	—	1.53	14.57	2.43	1.94	—0.71
18.59	8.32	3.87	—	1.01	13.78	2.49	2.11	—0.36

the range of variation is small (Table 3). It is also shown (Table 2) that if a wave is small when taken with one electrode (for instance, P_1[5] taken with the German silver electrode), it does not follow that another wave (e. g. R_1) taken with the same electrode is also small, when compared with like waves (R_1) taken with other electrodes. (R_1 taken with the German silver electrode for instance is the tallest of the R waves in Lead 1). That in the same lead, the height of a given wave (R_1 for instance) varies is due probably to the influence of respiration.

4. A comparison of curves taken at higher resistances is not essential in this study, for it is admitted that overshooting occurs at higher resistances, and likewise that the amount of overshooting differs with different metals. The lead electrodes are perhaps more satisfactory in this respect than other similar ones.

TABLE 3.—Limits of Ranges of the Corrected Averages

Wave	Lead	Limits	Range
P	1	0.90 and 1.02 mm.	0.12 mm.
P	2	0.93 to 1.25	0.32
P	3	0.33 to 0.87	0.54
Q	1	2.47 to 2.67	0.20
R	1	16.03 to 18.59	2.56
R	2	8.27 to 9.21	0.94
R	3	3.87 to 4.43	0.56
S	2	1.01 to 2.67	1.66
S	3	13.36 to 15.45	2.09
T	1	1.88 to 2.49	0.61
T	2	1.90 to 2.11	0.21
T	3	0.36 to 0.71	0.35

In view of the practical identity of the heights of the waves all the electrodes described may be used interchangeably. The electrodes used by us are recommended because their construction is at least as simple as any other, and of the electrodes which are fastened to the limb they are smaller and easier to apply. They are by far the most comfortable, and can therefore be kept in place during prolonged observations. They answer the requirement that with them a low resistance can be attained, and a low resistance is the most important criterion in establishing the usefulness of electrodes. It is by no means uncommon to obtain resistances as low as 500 ohms.
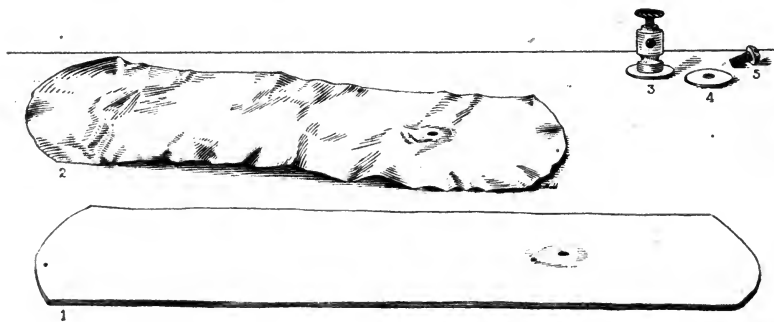
Fig. 1.—Electrode in use at Hospital of Rockefeller Institute. The lead foil, rubber sheet and binding post are shown separately.

SUMMARY

With all electrodes, electrocardiograms are deformed by overshooting of the string, when the resistance developed at the site of the application is high.

Electrodes of simple construction are described. Electrocardiograms taken with them are identical with those taken by other electrodes, when the resistances are below 2,000 and comparable.
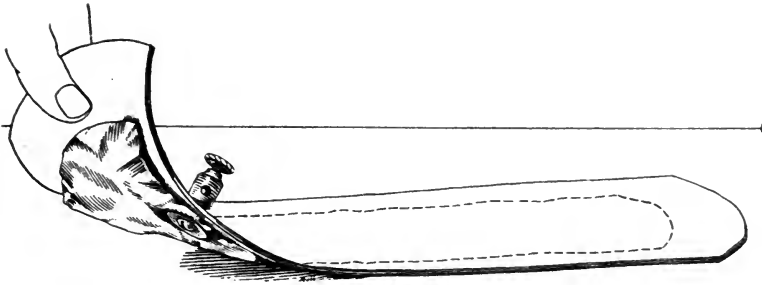
Fig. 2.—The electrode as assembled and ready for use.
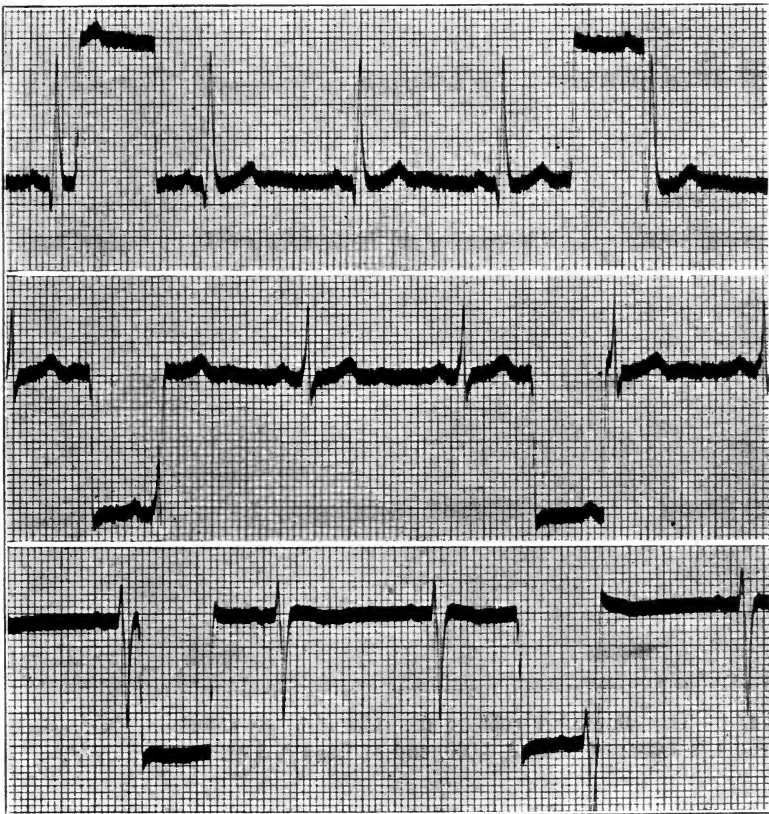
Fig. 3.—In all the electrocardiograms divisions of the ordinates equal 0.1 millivolt; divisions of the abscissae equal 0.04 second. The three usual leads are arranged from above downward. In each figure there are two deflections of about 20.0 mm. and of about 0.4 to 0.5 second duration. These are deflections caused by throwing 20 ohms into the circuit. This electrocardiogram was taken with lead electrodes before rubbing the skin with salt solution. The resistance of Lead 1 is 2,000; of Lead 2, 2,300; of Lead 3, 2,300 ohms.
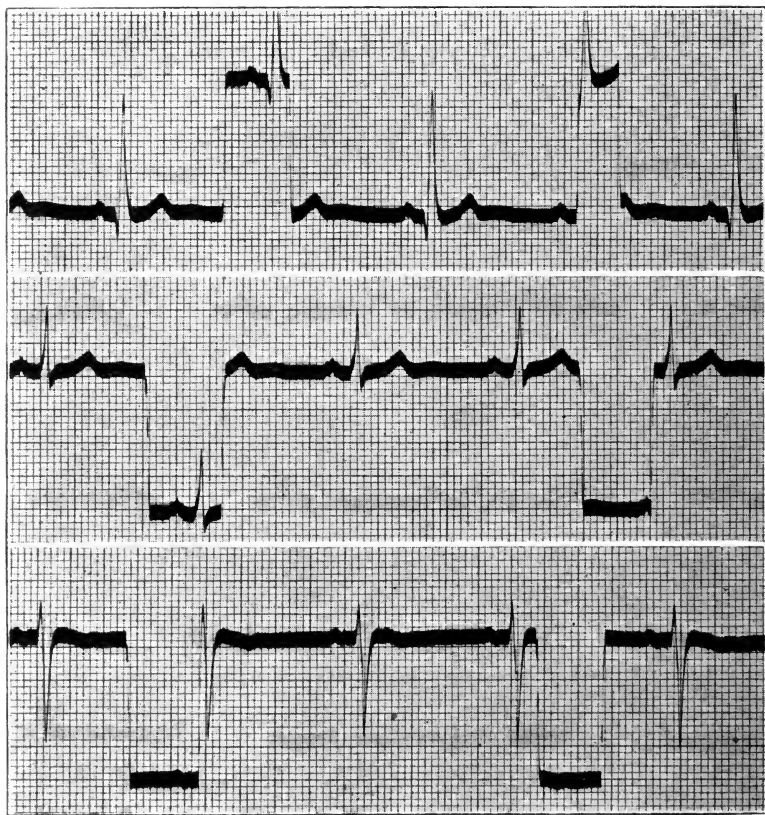
Fig. 4.—The same after rubbing the skin with salt solution. The resistance of Lead 1 is 1,000; of Lead 2, 1,000, and of Lead 3, 3,100 ohms.
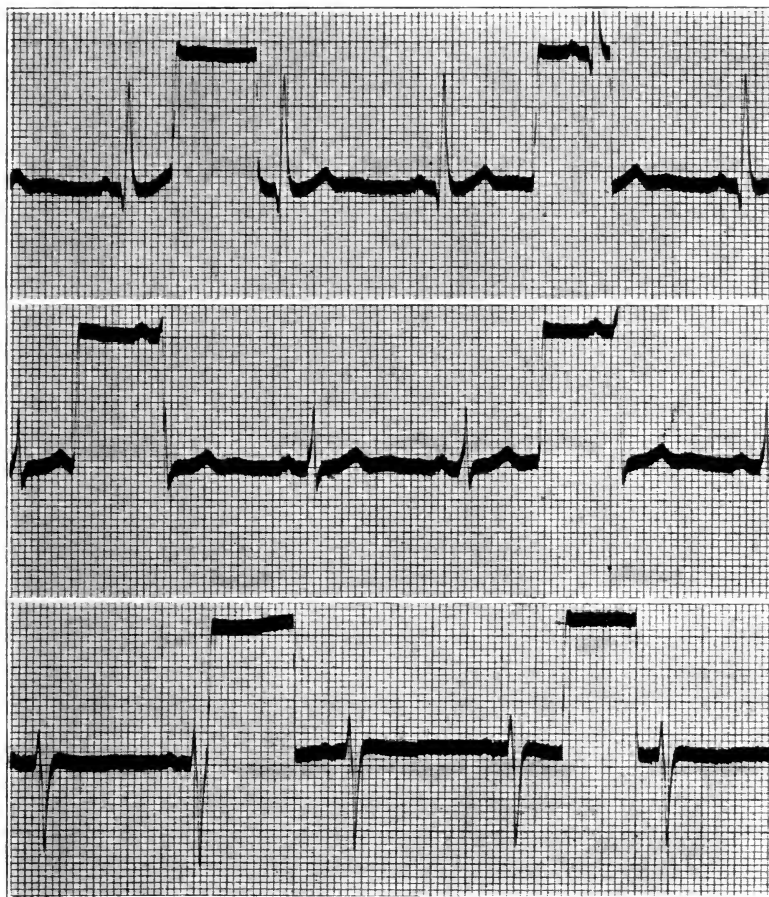
Fig. 5.—This electrocardiogram was taken with immersion nonpolarizable electrodes after rubbing the skin with salt solution. The resistance of Lead 1 is 2,500; Lead 2, 2,500, and Lead 3, 2,500 ohms.
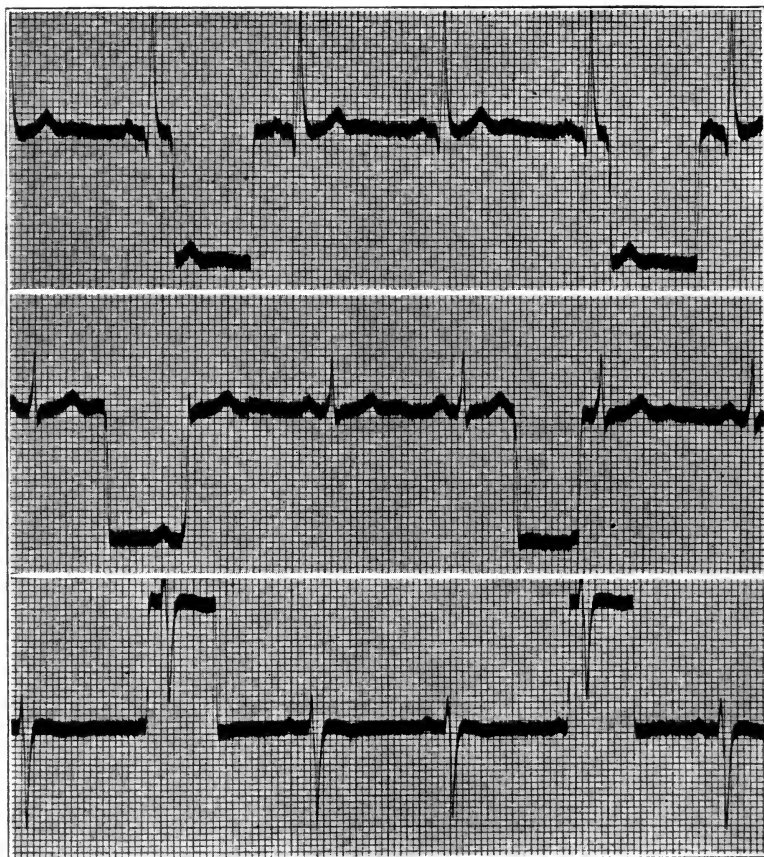
Fig. 6.—This electrocardiogram was taken with plate electrodes after rubbing the skin with salt solution. The resistance of Lead 1 is 2,300; of Lead 2, 2,300; of Lead 3, 1,400 ohms.
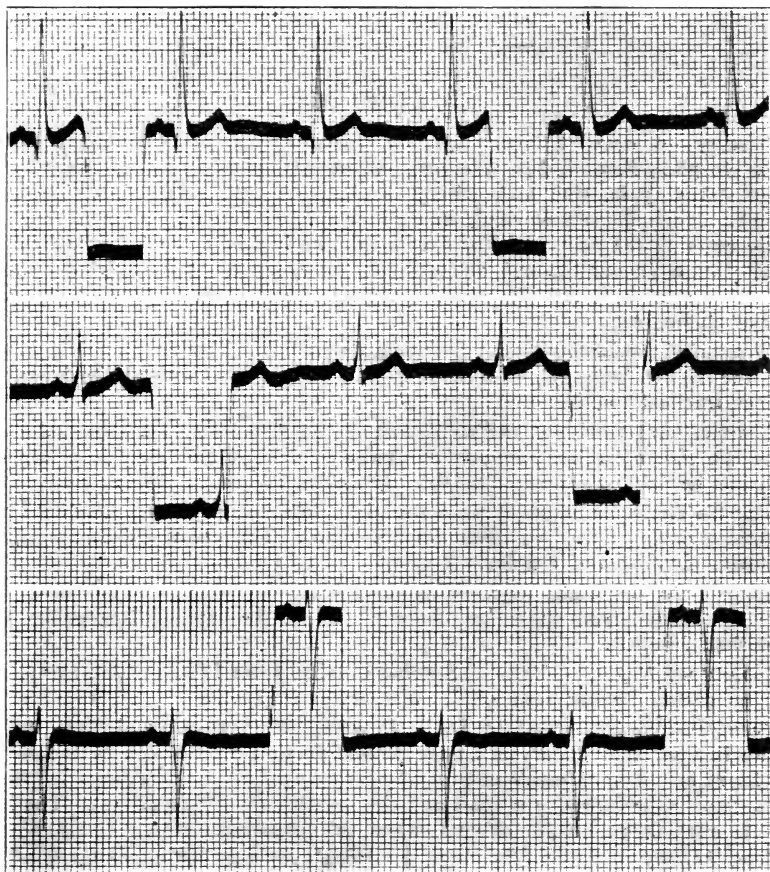
Fig. 7.—This electrocardiogram was taken with German silver electrodes after rubbing the skin with salt solution. The resistance of Lead 1 is 1,400; of Lead 2, 1,400; of Lead 3, 1,400 ohms.

FROZEN SECTIONS FROM A CASE OF PROTRUDING ANEURYSM OF THE ARCH OF THE AORTA

GEORGE WILLIAM NORRIS, A.B., M.D.

AND

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PHILADELPHIA

REPORT OF CASE

History.—A negro laborer, aged 39 years, was admitted to the Pennsylvania Hospital, Sept. 1, 1919 (service of Dr. Arthur Newlin), complaining of upper sternal pain, dull and aching in character and referred to the right scapula. He had been working intermittently, but had not taken to his bed before entering the hospital. For five months he had been troubled with cough, expectoration (never bloody) and dyspnea on exertion. His sleep was sometimes disturbed by pain. Nycturia (once or twice). No history of venereal disease obtainable.

Physical Examination.—Lies comfortably in bed. The left pupil is larger than the right; both pupils seem sluggish. The teeth are poorly kept. A distinct tracheal tug is noted.

Thorax.—Anteriorly, at the third costosternal juncture, is a spherical mass about the size of a hen's egg which pulsates visibly, and over it a systolic thrill can be felt. Expansion of the right chest is greatly diminished.

Heart.—The apex impulse is in the sixth interspace, 3 cm. outside of the left midclavicular line. No murmurs are heard. The radial pulses are equal, synchronous, slow and regular.

Lungs.—On the right side, posteriorly, bronchial breathing is heard and dulness is elicited from the spine of the scapula to the base, also egophony and diminished fremitus.

Laboratory Reports.—Urine: Specific gravity, from 1.020 to 1.030; no albumin; no casts. Leukocytes: 9,520. Wassermann: positive.

Roentgen-Ray Report.—(Dr. D. R. Bowen.) Fluoroscope and plate study: "There is a saccular aneurysm of the second portion of the arch of the aorta. The heart is not very much enlarged."

Anteriorly the lung is resonant and the breath sounds are distant. The left chest is normal, except for dilated superficial cutaneous veins.

Sept. 22, 1919.—Patient has been irrational for the last three days. The tumor mass has increased, now measuring 11 cm. in diameter. Respirations are difficult. Wiring of the aneurysm was discussed with Dr. J. H. Gibbon, but decided against.

September 23.—The patient's condition has gradually grown worse. Dyspnea, orthopnea and chest pain have necessitated the use of morphin. At 1 a. m. respirations became very laborious. Edema of the lungs was developing which was not checked by atropin or phlebotomy. Death at 2 a. m., apparently from pulmonary edema.

Having obtained possession of the (unclaimed) body through the courtesy of Dr. Addinell Hewson of the State Anatomical Board, the body was formalinized, frozen and cut in the usual manner.
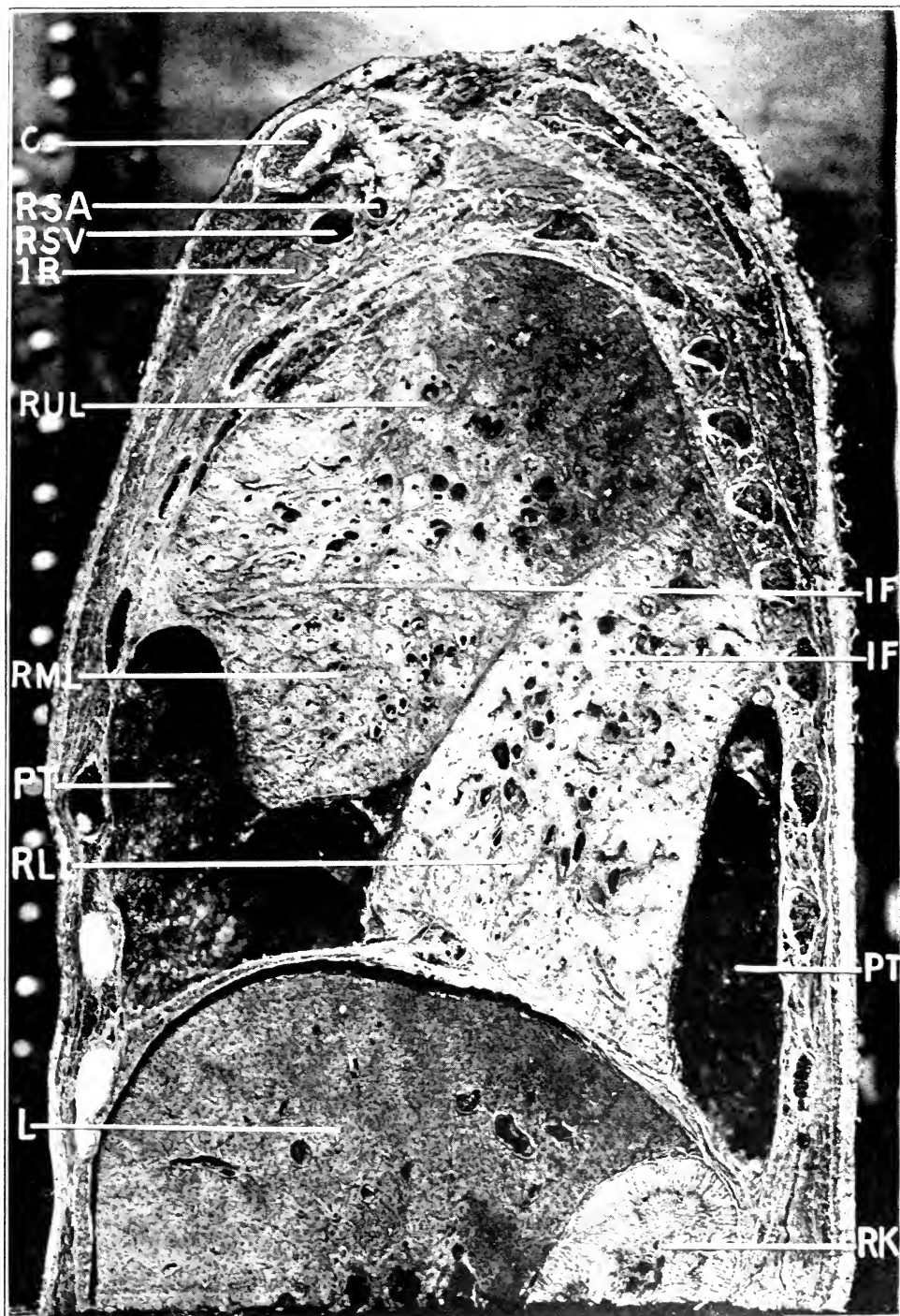
Fig. 1.—C, clavicle; RSA, right subclavian artery; RSV, right subclavian vein; 1R, first rib; RUL, right upper lobe; RML, right middle lobe; PT, PT, pleural transudate; RLL, right lower lobe; L, liver; RK, right kidney; IF, IF, interlobar fissures.
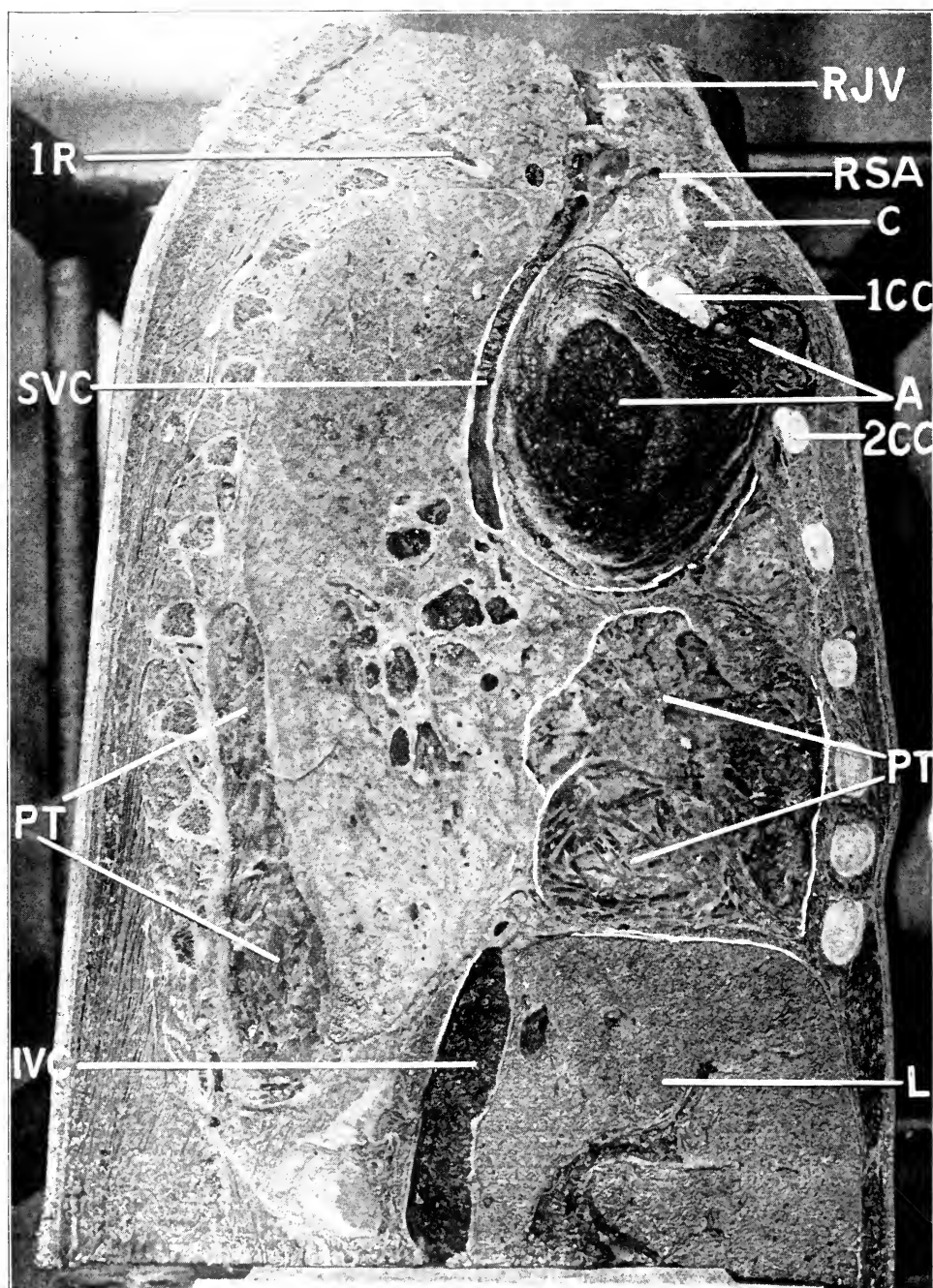
Fig. 2.—1R, first rib; SVC, superior vena cava; PT, PT, pleural transudate; IVC, inferior vena cava; L, liver; 2CC, 1CC, second and first costal cartilages; A, aneurysm; C, clavicle; RSA, right subclavian artery; RJV, right internal jugular vein.
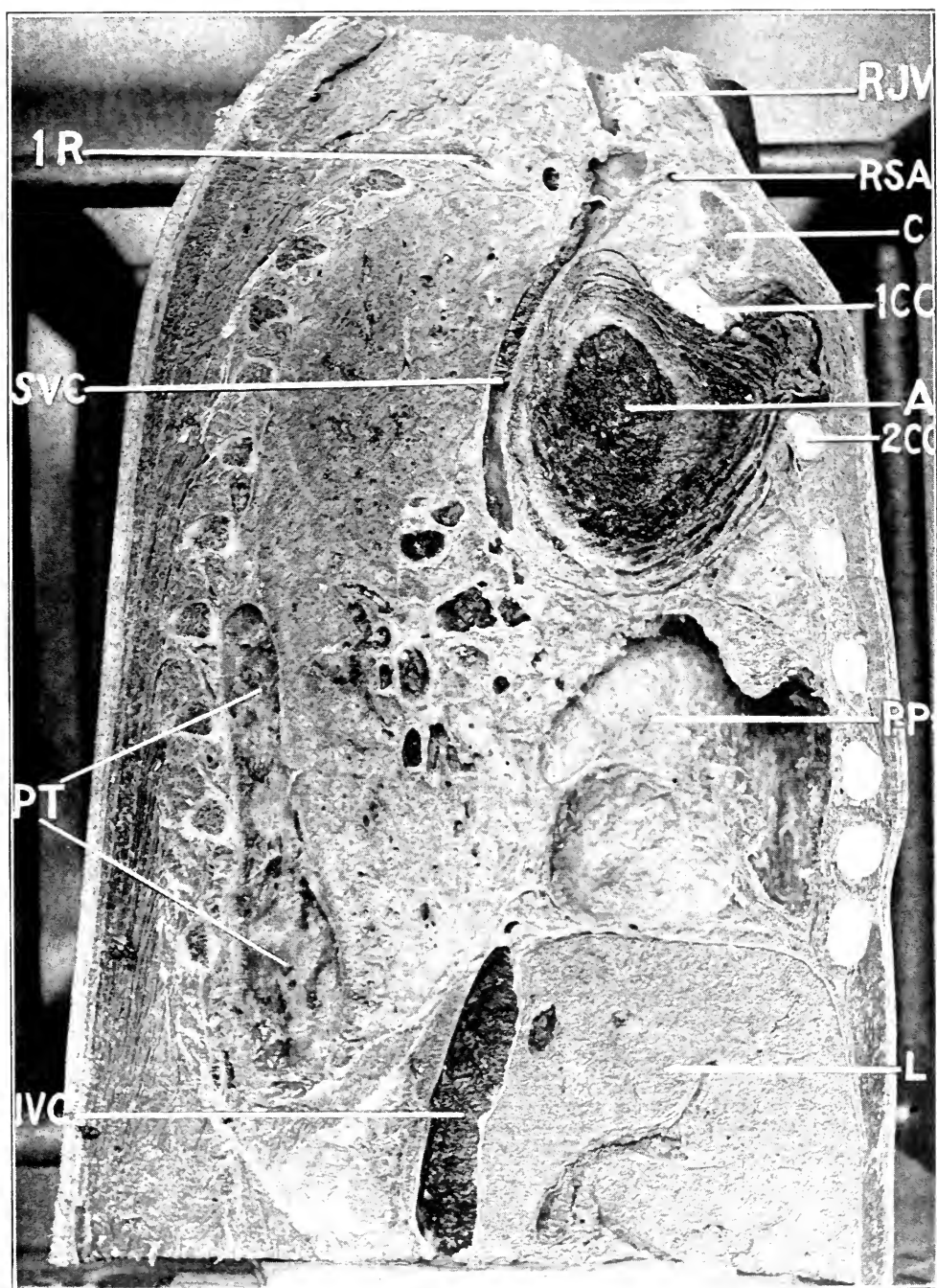
Fig. 3.—1R, first rib; SVC, superior vena cava; PT, pleural transudates; IVC, inferior vena cava; L, liver; P-P, pleuro-pericardium; 2CC, 1CC, second and first costal cartilages; A, aneurysm; C, clavicle; RSA, right subclavian artery; RJV, right interior jugular vein.
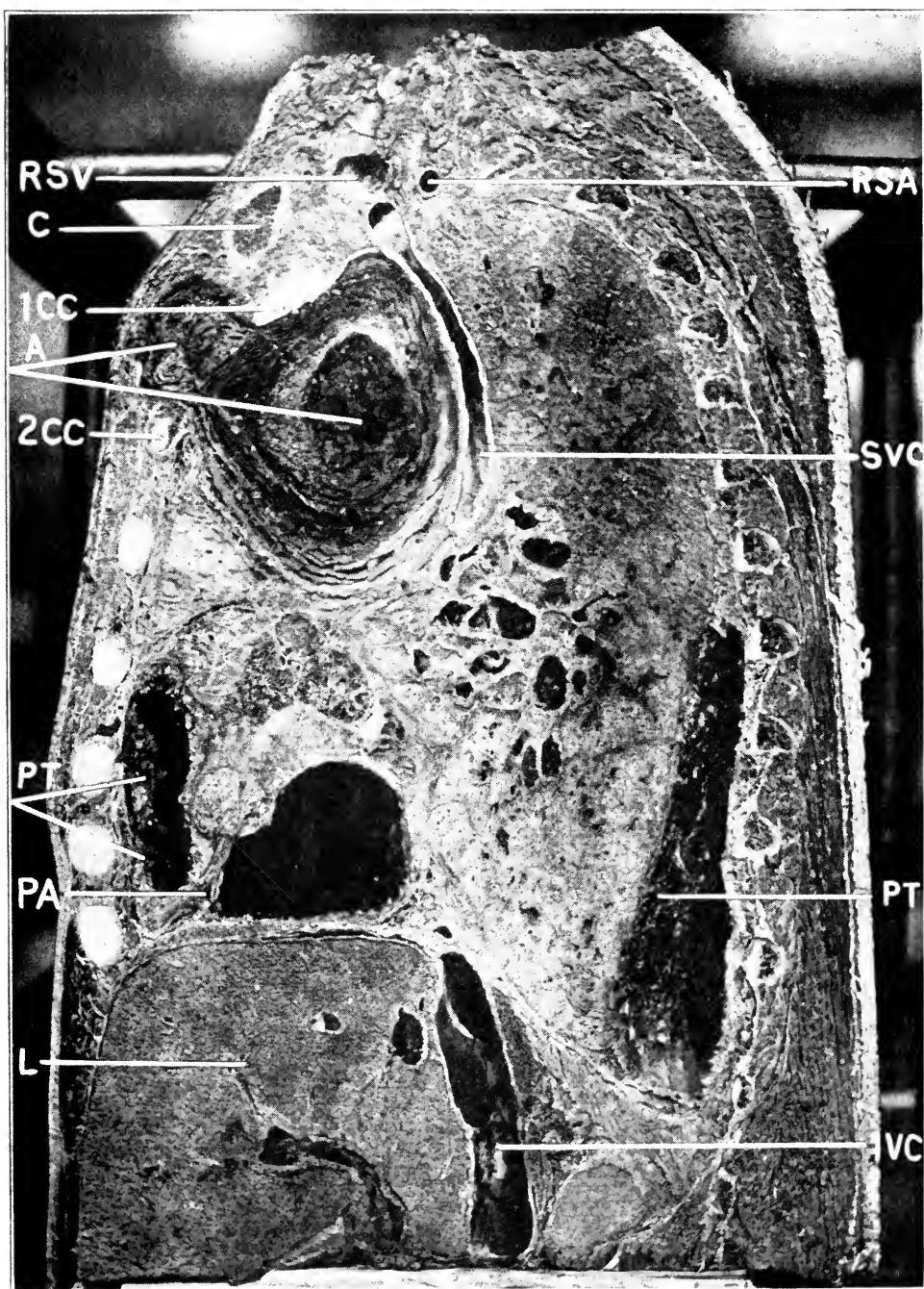
Fig. 4. RSV, right subclavian vein; C, clavicle; 1CC, 2CC, first and second costal cartilages; A, aneurysm; PT, PT, pleural transudate; PA, pleural adhesion; L, liver; IVC, inferior vena cava; SVC, superior vena cava; RSA, right subclavian artery.
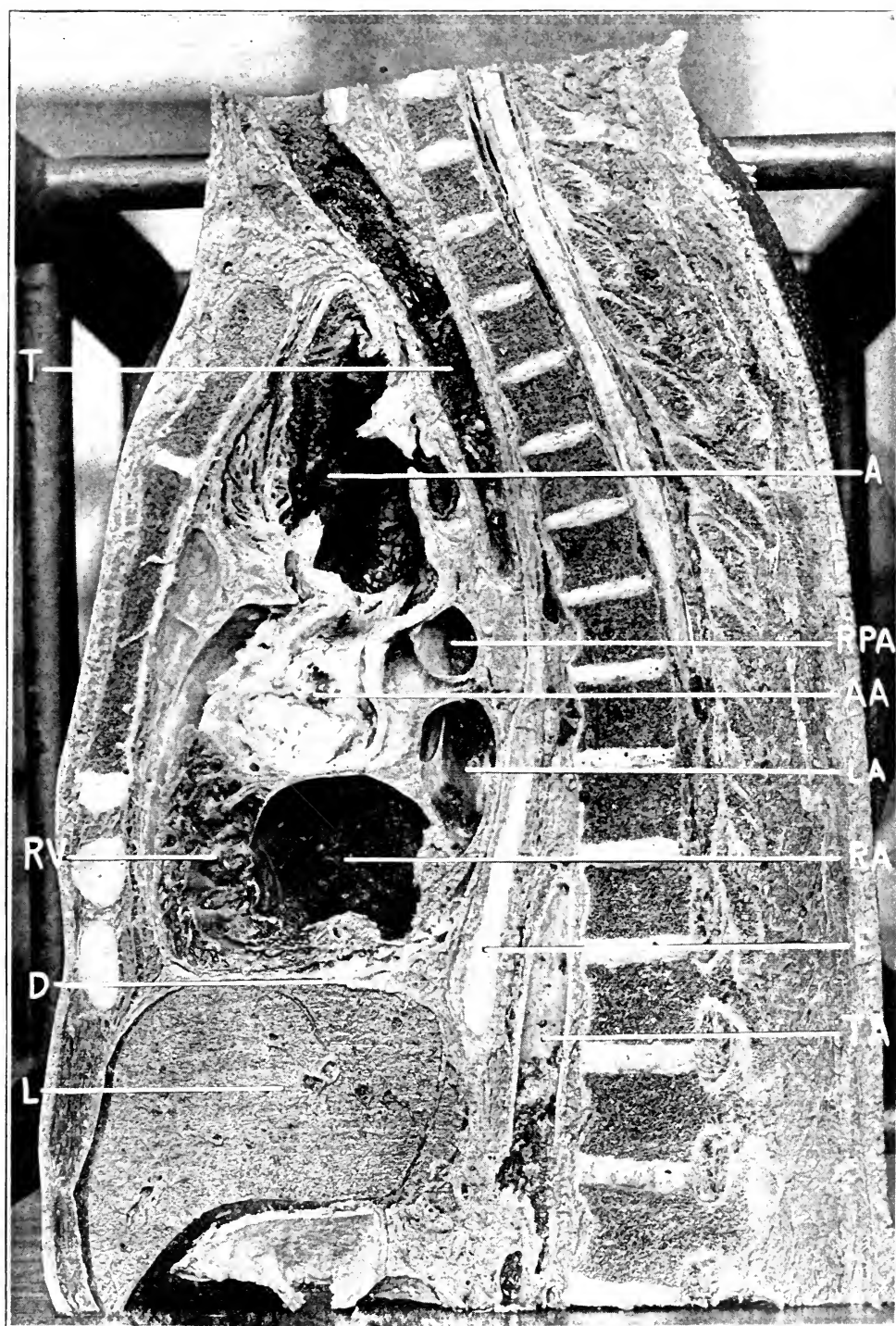
Fig. 5.—T, trachea; RV, right ventricle; D, diaphragm; L, liver; T.A, thoracic aorta; E, esophagus; R.A, right auricle; L.A, left auricle; A.A, ascending part of aortic arch; RP.A, right pulmonary artery; A, aneurysm.
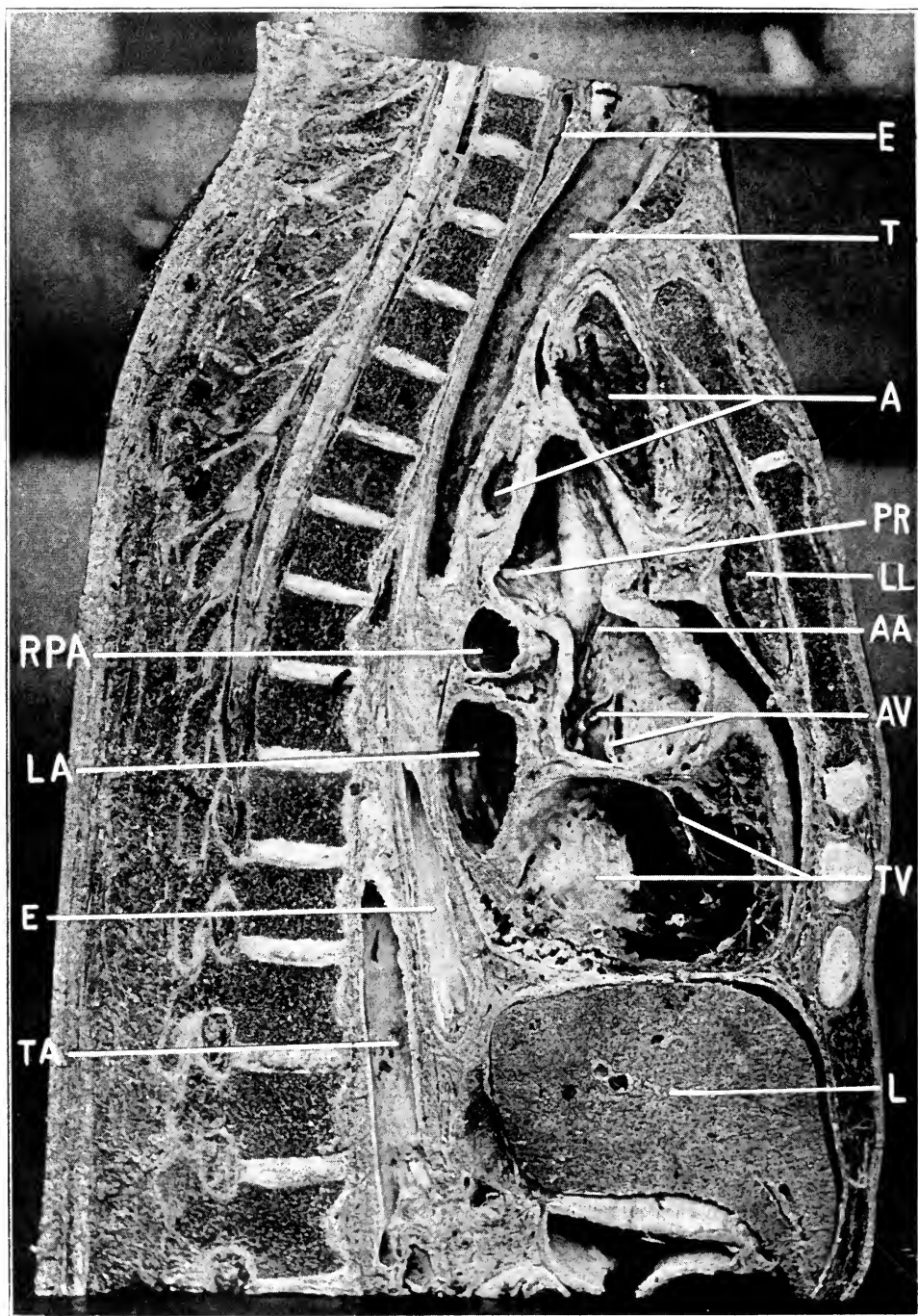
Fig. 6.—RPA, right pulmonary artery; LA, left auricle; E, esophagus; TA, thoracic aorta; L, liver; TV, tricuspid leaflets; AV, aortic leaflets; AA, ascending portion of aortic arch; LL, small portion of left lung; PR, probe in opening between aneurysm and trachea; A, aneurysm; T, trachea.
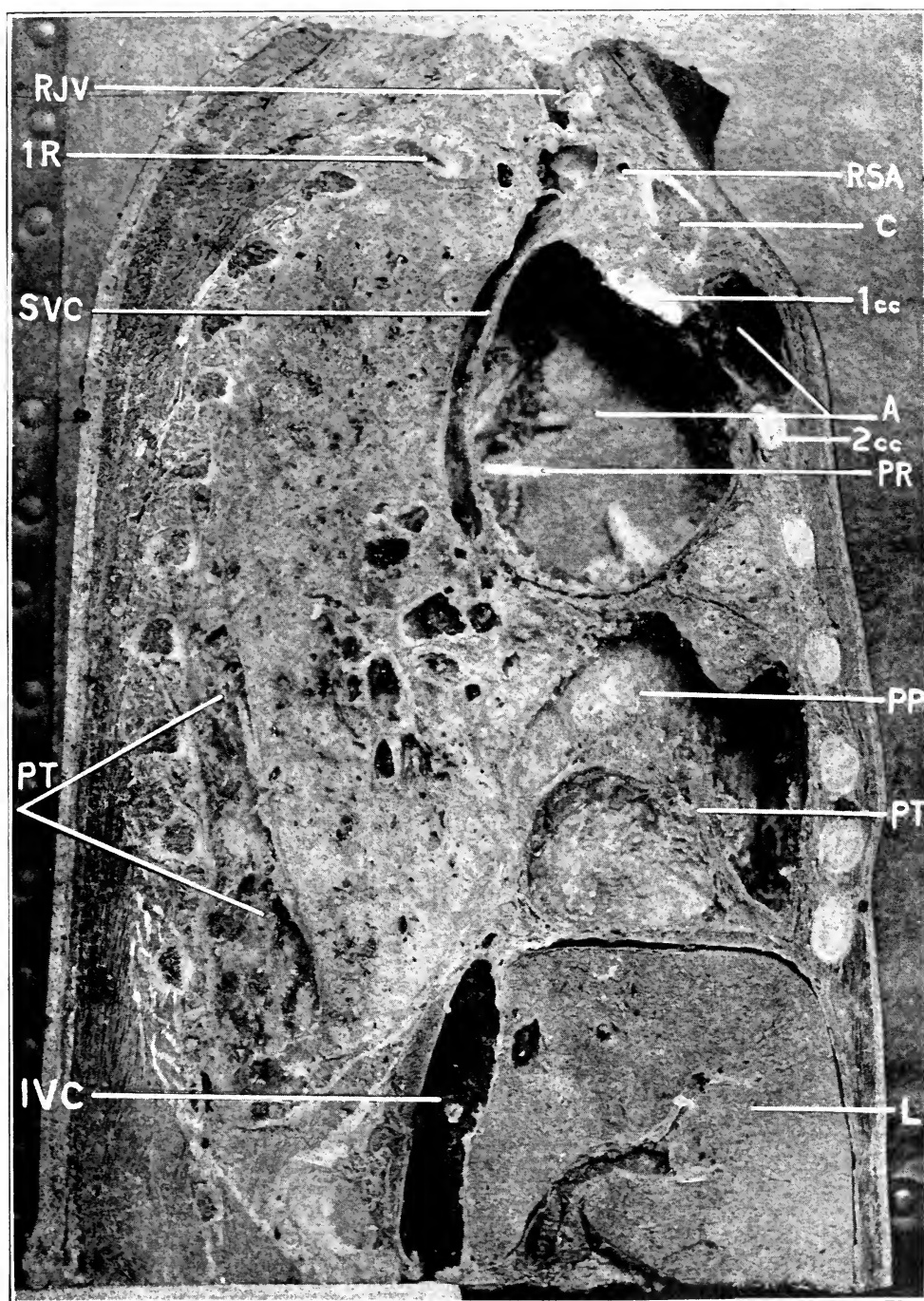
Fig. 7.—RJV, right internal jugular vein; 1R, first rib; SVC, superior vena cava; PT, PT, pleural transudate; IVC, inferior vena cava; L, liver; P-P, pleuro-pericardium; PR, probe in opening between trachea and aneurysm; 2CC, 1CC, second and first costal cartilages; A, aneurysm; C, clavicle; RSA, right subclavian artery.
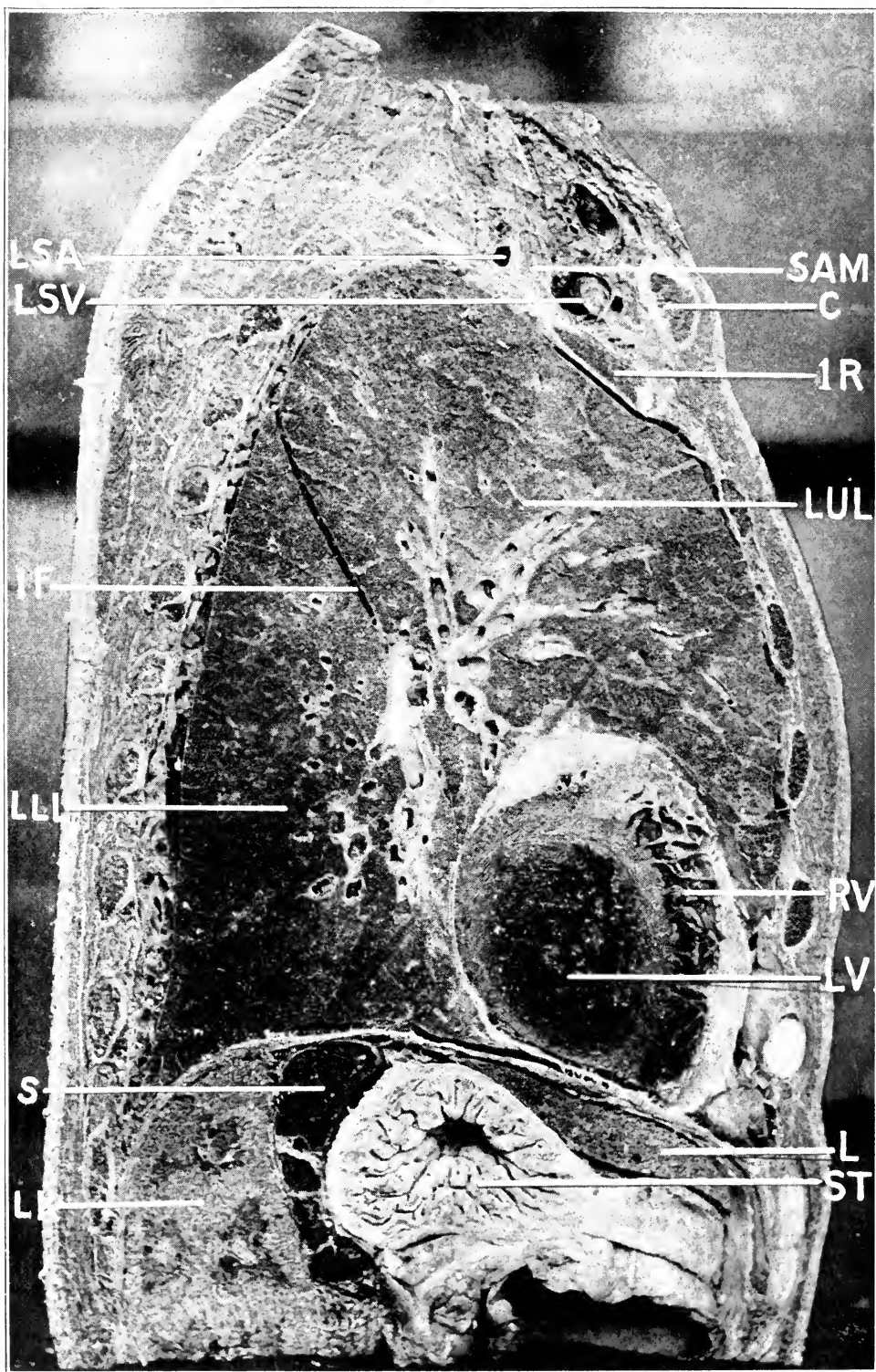
Fig. 8. LSA, left subclavian artery; LSV, left subclavian vein; IF, interlobar fissure; LLL, left lower lobe; S, spleen; LK, left kidney; ST, stomach; L, liver; LV, left ventricle; RV, right ventricle; LUL, left upper lobe; 1R, first rib; C, clavicle; SAM, scalenus anticus muscle.

DISCUSSION

Figure 1, which was cut approximately through the middle of the right lung, shows two pleural vomicae caused by loculation of an effusion. The lower pulmonary lobe is densely and firmly adherent to the central portion of the diaphragm, and the interlobar fissures show firm fibrous adhesions. The lung itself, in addition to atelectasis and compression of its lower portions, shows a widespread fibrosis which is strikingly in contrast to the left lung shown in Figure 8.

Inasmuch as the past medical history failed to indicate any antecedent pulmonary disease, such as pneumonia or pleurisy, one is forced to conclude that the fibrosis resulted from long standing hydrothorax, despite the fact that the general appearance would suggest an antecedent pneumonia complicated by an unrecognized empyema.

Figure 2, cut nearer to the median line, shows the pleural vomicae still filled with frozen serum (ice crystals) and a section of the aneurysm. The latter is filled with a laminated clot and protrudes between the first and second ribs. The superior vena cava immediately behind it is seriously encroached on, in contrast to the inferior vena cava, and explains the venous engorgement of the neck and head.

Figure 3 shows the same section, after the removal of the frozen serum from the pleural vomicae.

Figure 4 shows the next section, in which a dense, fibrous adhesion extends from the anterior portion of the lower lobe to the diaphragm, causing still another loculation of the pleural cavity. The liver immediately underlying this region is noticeably flattened.

Figure 5, the section of which passes through the middle of the sternum and the vertebral column shows the sacular character of the aneurysm. The ascending aorta is aneurysmal. Above this it retains approximately its normal size, to dilate again and to a much greater degree. It is partially filled with laminated clot and fresh blood clot. The trachea behind the aneurysm is filled with clot.

Figure 6, the other half of the median section (Fig. 5) well shows the first sacculation of the aneurysm, immediately above the aortic leaflets, as well as a second and third sacculation. The latter, the smallest, lies immediately in front of the trachea at the level at which the rupture occurred (Fig. 7).

Unlike a somewhat similar case previously reported,[1] the perforation did not occur at a point in the direct line of the blood stream. The trachea and the left auricle are both noticeably encroached on by the aneurysm. It will be noted that the sternum is intact, the aneurysm having protruded between the ribs.

1. Tr. A. Am. Phys. **32**:420, 1917.

Figure 7 (Fig. 3 with the aneurysmal clot removed) shows a match stick inserted into the perforation which opened into the trachea, which promptly became filled with blood as shown in Figure 5.

Figure 8, a section through the left lung shows a normal lung somewhat congested at the base. This cut should be compared with Figure 1, which shows extensive pulmonary fibrosis.

It is generally believed that in only about 50 per cent. of all cases of thoracic aneurysm does death occur by rupture.

This patient appeared to die from pressure and from exhaustion. Although no blood was coughed up, the trachea was filled with it, death occurring from suffocation due to rupture. It seems not unlikely that rupture may account for more deaths than purely clinical records, without a postmortem, would lead us to believe.

1820 South Rittenhouse Square.

RESULTS OF ANTEMORTEM LUNG PUNCTURES IN LOBAR PNEUMONIA

THEIR BEARING ON THE MECHANISM OF CRISIS [*]

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Typing of pneumococci in the sputum of patients suffering from lobar pneumonia was begun in this laboratory in March, 1919. In order to corroborate the results, lung punctures were performed at the same time and the organisms thus obtained were checked up with those in the sputum. As time went on, aside from this corroborative value, the results of the lung punctures appeared to us to have an interest from quite a different point of view, namely, as throwing some light on the nature of the mechanism of crisis. It is from this point of view that we are presenting our results. In so doing, we fully realize that the work itself is not original; nevertheless, it seems to be of some value both as confirming the results of our predecessors and as a stimulus possibly to others to attempt similar work. There seems to be some necessity for this, as there appears to be a general impression among clinicians that lung puncture is a hazardous procedure, apt to produce such complications as empyema; in answer to such objections and to allay such fears, we can say that we never have seen any unfavorable results, such as empyema, hemorrhage, etc., following lung puncture. It is only fair to state that one patient did die suddenly, but in this instance the chest was being tapped for suspected fluid, and a lung puncture was not being done intentionally. Such an unfortunate accident is, of course, to be encountered in any large series of chest taps, and, therefore, should not be considered as an objection to lung puncture.

A review of the literature shows that antemortem lung puncture has been a relatively infrequent procedure, though first done in 1883 by Leyden.

Leyden [1] found organisms in one out of three cases in which he performed lung puncture. That patient died.

Gunther,[2] suspecting pus, was rewarded by finding diplococci in the exudate withdrawn by puncture of the lung.

1. Leyden, I.: Deutsch. med. Wchnschr. 9:52, 1883.
2. Günther: Deutsch. med. Wchnschr. 9:52, 1883.

Talamon [3] performed postmortem lung punctures in nine cases, finding pneumococci in smears of the exudate in eight.

Patella [4] performed a series of punctures before and after crisis. In all those done before crisis the exudate contained a large number of pneumococci. Punctures done after crisis gave inconstant results, but in the exudate withdrawn by puncture during the hours immediately following defervescence, this author was able to recover viable pneumococci.

Tchistovitch [5] practiced punctures, inoculated the exudate into rabbits and mice and was able to convince himself that even after crisis one can withdraw from the lungs by puncture an exudate containing not only viable but virulent diplococci. Therefore, he said, crisis cannot depend on the destruction of all the diplococci in the lung. He went on to say that crisis occurs when toxin formation by the pneumococci ceases, due to their being taken up by the phagocytes, and kidney elimination increases.

Rosenow [6] made forty-eight punctures in twenty-seven cases to study the bacteriologic and cellular content of the lung exudate more especially from a point of view of phagocytosis. Of the forty-eight, twenty-six yielded growths of pneumococci in pure culture; twenty-two were sterile. Positive punctures were obtained at all stages of the disease, but the percentage of positive results was much higher in the early stages of favorable cases and throughout the course in those patients that died. Early in the course of fatal and nonfatal cases the number of positive results was the same; in favorable cases the number gradually diminished as crisis was reached. Only six out of twenty punctures during or after crisis yielded organisms, and only a few colonies in each, while in patients who died the number became progressively greater as death approached.

The technic of lung puncture is very simple. In selecting the point to puncture the area of maximum solidification as determined by physical signs is chosen. After cleansing the skin with alcohol and iodin, local anesthesia is produced with 0.5 per cent. procain. A No. 16 needle is then introduced between the ribs, through the pleura and into the lung tissue to the depth of about one inch. Negative pressure is then maintained with a 10 c.c. or 20 c.c. syringe and the needle slowly withdrawn. In this way a few drops of bloody fluid are obtained and may then be cultured in broth and on blood agar and a film made on a slide.

3. Talamon, M. le D.: Bull. Soc. Anat. de Par. **63**:475, 1883; also Progrès méd. **11**:281, 301, 1883.

4. Patella, V.: Attr. d. R. Academia di Roma, **4**: 1888.

5. Tchistovitch, N.: Ann. de L'Inst. Pasteur **18**:304, 1904.

6. Rosenow, E. C.: J. Infect. Dis. **8**:500, 1911.

For the sake of brevity, we designate lung punctures yielding living pathogenic organisms which were cultivated and studied as "positive lung punctures," those which yield sterile cultures as "negative lung punctures." From a direct smear of the exudate little of value was learned; usually, however, a smear which failed to show organisms was associated with negative cultures also.

In Table 1, where the positive and negative punctures are charted according to the day of disease on which they were performed, it will be noticed that the two series run almost parallel in this respect.

TABLE 1.—RECORD OF POSITIVE AND NEGATIVE PUNCTURES

	Day of Disease															Total	Mortality
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15		
Positive lung punctures.....	0	1	5	4	7	4	5	7	5	1	2	0	0	0	1	42	43.00%
Negative lung punctures....	..	1	3	4	3	5	5	3	1	2	1	1	0	0	2	31	6.45%

Table 2 takes into account the organism obtained from punctures and also shows which of the patients died (those indicated by the lower line of figures in each square). The abnormally high mortality for the individual type and for this whole group is quite striking (six of the Type 1 patients who recovered were given treatment with antipneumococcus serum). It is also interesting to note that the mortality in the cases yielding positive punctures before the sixth day is 23.5 per cent., whereas in those positive on and after the sixth day the mortality is 56 per cent.

Table 2 also illustrates the negative punctures, the bacteriologic grouping being obtained from the sputum examination. Only two of these patients died — one five days and the second three days after the puncture — each having an extension of the pulmonary lesion into a fresh lobe. An adequate explanation for the occurrence of these two negative punctures is not at hand unless one admits the possibility of local recovery in the face of an active and eventually fatal process elsewhere. Further evidence that this may occur is seen at necropsy in cases in which one lobe is undergoing resolution while another is in the stage of red or gray hepatization.

A point which is not illustrated in these tables is that positive lung punctures were obtained on every day of the disease including the period of critical fall of the temperature and twice after the temperature had reached normal. On the other hand, one negative puncture four days before crisis, two negative punctures three days before crisis and six negative punctures two days before crisis show quite clearly that, in cases which are going on to recovery, the organisms may diminish to a great extent some time before crisis occurs. If, as has been claimed, a sudden destruction of the organisms takes place at the

TABLE 2.—DAY OF DISEASE ON WHICH PUNCTURE WAS PERFORMED, AND MORTALITY

Positive Lung Punctures

	Day of Disease															Well	Dead	Total	Per Cent. of Cases	Mortality, Per Cent.
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15					
Pneumococcus Type I	:	:	3	2	4	2	1 / 1	1	1 / 1	: / 1	: / 1	:	:	:	: / 1	14	4	18	43	22
Pneumococcus Type II	:	: / 1	: / 1	1	1	: / 2	: / 1	2 / 1	: / 1	:	:	:	:	:	:	4	7	11	26	64
Pneumococcus Type III	:	:	:	:	: / 1	:	: / 1	:	: / 1	: / 1	: / 1	:	:	:	:	1	4	5	12	80
Pneumococcus Type IV	:	:	1	1	: / 1	:	: / 1	1 / 1	1	:	:	:	:	:	:	4	3	7	17	43
Pneumococcus Type (?)	:	:	:	:	1	:	:	1	:	:	:	:	:	:	:	1	:	1	2	0
Well	:	:	4	4	5	2	1	5	3	1	:	:	:	:	:	24				
Died	:	1	1	0	2	2	4	2	2	1	2	:	:	:	1		18			
Total	:	1	5	4	7	4	5	7	5	1	2	:	:	:	1	:	:	42	100	43

Negative Lung Punctures

	Day of Disease															Well	Dead	Total	Per Cent. of Cases	Per Cent. of Cases	Mortality, Per Cent.
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15						
Pneumococcus Type I	:	1	1	:	1	1	1	2	:	:	:	:	:	:	:	7		7	29	23	0
Pneumococcus Type II	:	:	:	1	:	:	3	:	:	2	:	:	:	:	:	6		6	25	19	0
Pneumococcus Type III	:	:	:	1 / 1	:	:	:	1	:	:	:	1	:	:	1	4	1	5	21	17	20
Pneumococcus Type IV	:	:	:	:	:	:	:	:	1	:	1	:	:	:	1	5	1	6	25	19	16
Nonhemolytic streptococci	:	:	1	:	:	2 / 1	:	:	:	:	:	:	:	:	:	1	1	1		3	0
Unknown	:	:	1	1	2	1	1	:	1	:	:	:	:	:	:	6		6		19	0
Well	1	1	3	3	3	4	5	3	1	2	1	1	:	:	2	29					
Died	:	:	1	1	:	1	:	:	:	:	:	:	:	:	:		2				
Total	:	1	3	4	3	5	5	3	1	2	1	1	:	:	2	:	:	31	100		6.5

The lower line of figures in each square represent the deaths.

time of crisis, positive lung punctures should be obtained with great regularity up to a short time before crisis in every case and not after crisis.

The fact which interests us most is that the number of organisms may begin to diminish fairly early in the disease, even three or four days before crisis in favorable cases, but fails to diminish throughout the course of cases which end in death. According to our conception, the organisms may be all killed twenty-four or more hours before crisis, or may continue to exist twenty-four hours after crisis. Thus the two mechanisms, i. e., bactericidal and detoxifying, are somewhat independent of one another, the second taking place at a given time after the first has gained control of the infection. (A pseudocrisis may even occur before the infection is properly under control.) As the organisms cease, then, to dominate the situation by their active growth in the lung, the detoxifying mechanism has a chance to become efficacious. Detoxication may occur in three ways: (1) By a cessation in toxin production; (2) by an increase in the antitoxic bodies to a point sufficient to neutralize the toxin as fast as it is produced, and (3) by a conversion of the toxic into nontoxic products. That the two mechanisms mentioned above — bactericidal and detoxifying — exist is by no means a new thought. But we offer this argument as a further point in favor of their existence.

The literature, since the discovery of the pneumococcus, has been filled with accounts of futile attempts to isolate pneumotoxins and produce antitoxins. G. and F. Klemperer,[7] as early as 1891, described the satisfactory use of serum in curing rabbits infected with pneumococcus and ascribed the results to the antitoxic properties of the serum. It is unnecessary here to review the entire literature on this subject. Suffice it to say that the consensus of opinion today [8] is that the pneumococcus contains preformed anaphylatoxin which is also hemolytic for red blood cells, and which is mildly antigenic. The antiserum formed by this anaphylatoxin (proteotoxin) cannot be used to produce passive immunity and is thought of little practical importance in the mechanism of recovery from pneumonia. The humoral and cellular activities described by various workers were well reviewed by Wadsworth [9] in 1912. The important agencies which had been shown to exist were serum bacteriolysis (slight), bactericidal property of whole blood (slight), increase in phagocytosis by the opsonins and bacteriotropins; and agglutinins and precipitins. Since that time anti-

7. Klemperer, G. and F.: Berlin klin. Wchnschr. **28**:833, 869, 1891. (Therap. Gaz., Aug.)

8. Cole, R.: New York M. J. **101**:1, 59, 1915. Rosenow, E. C.: J. Infect. Dis. **9**:190, 1911. Cole, R.: J. Exper. Med. **20**:346, 1914. Clough, P. W.: Johns Hopkins Hosp. Bull. **26**:37, 1915. Weiss, C., and Kolmer: J. Infect. Dis. **22**:469, 1918. Solis-Cohen, Weiss and Kolmer: J. Infect. Dis. **22**:476, 1918.

9. Wadsworth, A. B.: J. Exper. Med. **16**:54, 1912.

blastic immunity [10] has been demonstrated and discussed, sensitizing antibodies present in the blood before but not after crisis [11] have been claimed and the action of various chemicals in conjunction with immune serum has been demonstrated.[12]   Studies on the action of immune serum [13] administered to animals in which a pneumococcus septicemia is produced have led to the belief that the activities of the serum are due to agglutination of the organisms and bacteriotropic power of the serum.   More recently the mechanism of the effect of whole blood [14] of animals naturally immune or actively and passively immunized has been shown to depend on the opsonization of the pneumococci by the immune serum and the phagocytosis of the organisms by the poly-nuclear leukocytes.   But none of these factors offers a satisfactory explanation of the phenomenon of crisis.

From a somewhat different point of view the effect of the acid pro-duced in the course of normal growth of the pneumococcus [15] has been offered as cause for the death of the organism and activating of the proteolytic enzymes.[16]   Following the lead of Vaughan,[17] a great deal of most suggestive work on the toxic split products of the various proteins has been done.   Whether these toxic products are formed by partial splitting of the pneumococcus protein, the pneumonic exudate proteins, or the serum proteins has not been cleared up, but Petersen and Short [18] favor the lung exudate as the source.   Jobling, Petersen and Eggstein [19] suggest, however, that in the production of crisis the rapid death of a large number of pneumococci takes place, thus making possible the rapid and complete action of the ferment unhindered by antiferment and toxic by-products of bacterial growth.   The results obtained by these and other workers studying pneumonic blood and pneumonic exudate from a biochemical point of view, further strengthen the possibility that the toxemia in pneumonia is due to the constituents of the lung exudate, and that detoxication is due to an increase or alteration in ferment action whereby these toxic products

10. Dochez, A. R., and Avery, O. T.: J. Exper. Med. **23**:61, 1916.

11. Weil, R., and Torrey, J. C.: J. Exper. Med. **23**:1, 1916.

12. Lamar, R. V.: J. Exper. Med. **26: 27:** 1911. Kolmer, J. A., and Stein-field, E.: J. Infect. Dis. **22**:492, 1918.

13. Bull, C. G.: J. Exper. Med. **22**:457, 484, 1915.

14. Bull, C. G.: J. Exper. Med. **31**:233 (March) 1920.

15. Lord, F. T., and Nye, R. N.: J. Exper. Med. **30**:389 (Oct.) 1919. **Avery,** O. T., and Cullen, G. E.: J. Exper. Med. **30**:359 (Oct.) 1919.

16. Lord, F. T.: J. Exper. Med. **30**:379 (Oct.) 1919. Lord, F. T.: J. A. M. A. **73**:1364 (May 10) 1919.

17. Vaughan, V. C., V. C. Jr., and J. W.: Protein Split Products, Philadel-phia, Lea and Febiger, 1913.

18. Petersen, W., and Short, C. A.: J. Infect. Dis. **22**:147, 1919.

19. Jobling, J. W.; Petersen, W., and Eggstein, A. A.: J. Exper. Med. **22:** 568, 1915.

are rendered nontoxic. Weiss assumes a sudden destruction of large numbers of organisms at a time when the greatest amount of pneumotoxin and hence of toxin albumoses, of proteoses, etc., exists. He speaks of this as the period of crisis. We do not believe that this sudden destruction of organisms plays a part in crisis. We believe that a second mechanism, namely, that which serves to neutralize or destroy the toxic substances, acts, to a large extent, independently. The rate of development of the antibacterial bodies, on the one hand, and the antitoxic mechanism on the other, may occur simultaneously or not, according to factors which influence their separate production differently. Thus an early destruction of the organisms would leave little to be undertaken by the antitoxic mechanism whereas a late checking of the bacterial growth would require a much more active antitoxic effort on the part of the patient. Blake and Cecil,[20] from observations of a somewhat similar nature during the course of their work on experimental pneumonia in monkeys, suggest the possibility of a dual mechanism: one humoral, the other local and possibly biochemical in nature. Our conception differed slightly from theirs in that we believe the humoral reaction has a definite influence on the local pulmonary lesion and thus makes possible the fulfillment of the second mechanism, which is of a detoxifying nature and may or may not be entirely local.

There are certain facts that make the presence of a toxin in lobar pneumonia seem possible. In lobar pneumonia we have a local process with general symptoms and with lesions in the important organs. Microscopically, in cases of lobar pneumonia we find definite necroses in the liver, suprarenal, pancreas and kidney; lesions definitely toxic in origin, not due to the actual presence of the organisms, but caused by a toxin in the general circulation in every way analogous in type to the lesions seen in diphtheria. We know that this type of lesion can be produced by a bacterial exotoxin, but whether it can also be caused by a so-called proteotoxin (anaphylatoxin) or by toxic split products derived from the host's proteins has yet to be definitely demonstrated.

There are many explanations for the failure to demonstrate a toxin in the blood or lung exudate of a patient suffering from pneumonia; as for instance:

1. That the toxin is fixed by the tissues (or when standing in vitro combines with antibodies).

2. That there is such a thing as "species specificity" in toxins; i. e., that the toxin produced in the lung of a human being is toxic only for man, since it is formed from the proteins peculiar to man.

Meanwhile, the nature of the toxin remains undetermined. We know that there is no demonstrable soluble pneumotoxin. We know

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20. Blake, F. G., and Cecil, R. L.: J Exper. Med. **31**:460, 480 (April) 1920.

that the proteotoxin of the pneumococcus plays but a small part in causing the symptoms of toxemia, and we know that similar symptoms are caused by autolysis of aseptic tissue. This lends plausibility to the suggestions of Cole [21] and Jobling, Petersen, Eggstein and others, that the higher split proteins from the lung exudate are responsible for the toxemia in pneumonia. The possibility of a "species-specific" toxin formed by the growth of the pneumococcus in the lung exudate must still be considered. If a toxin exists, the production and importance of an antitoxin are pressing problems.

A solution to these questions is being sought at present but too little progress has as yet been made to justify a report.

SUMMARY

Study of lung punctures performed at different stages of lobar pneumonia, shows that the death of the organisms in the lung does not occur, in every case, at the time of crisis, but may occur several days before or after crisis. This leads to the belief that the anti-bacterial forces may proceed at one rate of speed while the detoxifying mechanism is going on at a different rate. The nature of the toxic substance in lobar pneumonia is imperfectly understood but the demonstration of toxic split proteins does not finally rule out the possibility of a true toxin-antitoxin reaction.

CONCLUSIONS

The death of the pneumococcus is not the factor which causes or initiates crisis.

The antibacterial and detoxifying mechanisms act, in a measure, independently.

21. Cole, R.: Arch. Int. Med. **14**:56 (July) 1914.

BODY WEIGHT IN TWO HUNDRED AND TWENTY-NINE ADULTS

WHICH ·STANDARD IS THE BEST?

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PROBLEM

It is rare for clinicians to recognize that medicine, as a whole, profits more by normal standards than by scattered observations of interesting pathologic cases. This is Benedict's judgment,[1] and Galton's [2] appears to have been much the same: "Variations of weight are the surest guides to health. . . . Dangerous illnesses may be avoided, and even life preserved." Such illnesses may be outspoken, like malnutrition in children, thyrotoxicosis and tuberculosis; also diabetes and obesity. Or the disease may be insidious, in which case the weight abnormalities are apt to be called defects without obvious cause. Such defects have been alarmingly frequent in recent military examinations. And not only frequent, but surprisingly important. ·For instance, if we are conservative and consider not the incidence among draftees but only the actual rejections, we find that overweight ranks second among the prominent causes of rejection, as detailed in Table 1.

TABLE ·1.—PHYSICAL CAUSES OF REJECTION

Causes of Rejection in Order of Frequency	By Seven Local Boards for the Army[3]	By the Navy and Marine Corps[3]	By the Total Draft for the Army[4]
	No. examined......7,611	No. examined.....82,592	No. examined..2,510,591
	Percentage of Examinees Rejected	Percentage of Examinees Rejected	Percentage of Examinees Rejected
1	Eyes.............. 6.0	Eyes.............. 11.4	Heart............. 4.3
2	Teeth............. 4.8	Underweight....... 6.5	Underweight....... 2.6
3	Underweight....... 4.6		
15 etc.	Overweight........ 0.4	Overweight not given	Obesity........... 0.17

The literature furnishes an embarrassing variety of standards by which to judge whether the weight of a given person is within normal

1. Benedict, F. G.: Boston M. & S. J. **181**:109, 117, 118 (July 31), 1919.
2. Galton, F.: Life History Album, London, 1884, p. 2.
3. Fisher, I., and Fisk, E. L.: ·How to Live, Ed. 15, New York and London, 1919, p. 400, 258.
4. Love, A. G., and Davenport, C. B.: Defects Found in Drafted Men, Printed for Senate Committee on Military Affairs, Washington, 1919, p. 71.

limits. To enable the physician or statistician to choose between these methods is the main object of this paper. The plan has been to collect measurements and actual weights on a series of normal individuals, then to predict the weights for these men by means of various standards, and finally by comparing these predicted weights with the actual weights to compute the error made by each standard.

INDIVIDUALS OBSERVED

The first series was abruptly terminated by entry into service of one of the authors, and was, therefore, reported at the time.[5] It is summarized in Table 7, together with some new calculations based on the original data. But this earlier series comprised only twenty subjects, and so it was thought desirable to assemble a second group. This was done in the intervals between regular work in the U. S. Army Base Hospital 76, mostly in France, while the extensive computations have been carried out since leaving the service. This second series comprises 229 soldiers, all from the personnel of Base Hospital 76. They were all born in the United States, mostly in Maryland and Pennsylvania. Most of them were inducted at Fort Oglethorpe in June, 1918, and mobilized as this hospital unit at Camp Devens in July, 1919. At that time they were weighed naked, measured and examined physically by the medical officers of the unit, in the hope of excluding some on the ground of possible defects overlooked in the hastier examination at enlistment. Incidentally, the number of positive Wassermanns in 200 tests was only one. The unit sailed from New York August 31, spent about a week in England, and was on duty in Vichy, Allier, France, from the latter part of September until after the time of the second weighing in January, 1919. Some of the original members had meanwhile been separated from the unit, but all who had been weighed twice at the six months' interval are included in this report. Nobody was excluded by preconceived notions on our part as to the typical man. The series is, therefore, unselected, except that males of military age who happen not to fit the army standard are not represented. This fact constitutes a technical defect, as pointed out by Hoffman, but the advantage accrues to a method other than that championed in this paper. Accordingly, we have assumed these to be fair samples of American-born young men, and as such to be suitable controls by which to test the accuracy or error of different methods for predicting weight.

The gist of this test is that Bornhardt's standard is the most accurate, closely followed by the Army and insurance tables; while

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5. Gray, H., and Gray, K. M.: Normal Weight, Boston .M. & S. J. **177**:894 (Dec. 27) 1917.

Guthrie's, Broca's and von Noorden's give much less satisfactory results. This is shown graphically in the accompanying chart, and is detailed numerically in Table 9. The casual reader, therefore, may well omit the following minutiae as to method, and skip to the conclusions at the end of the paper.
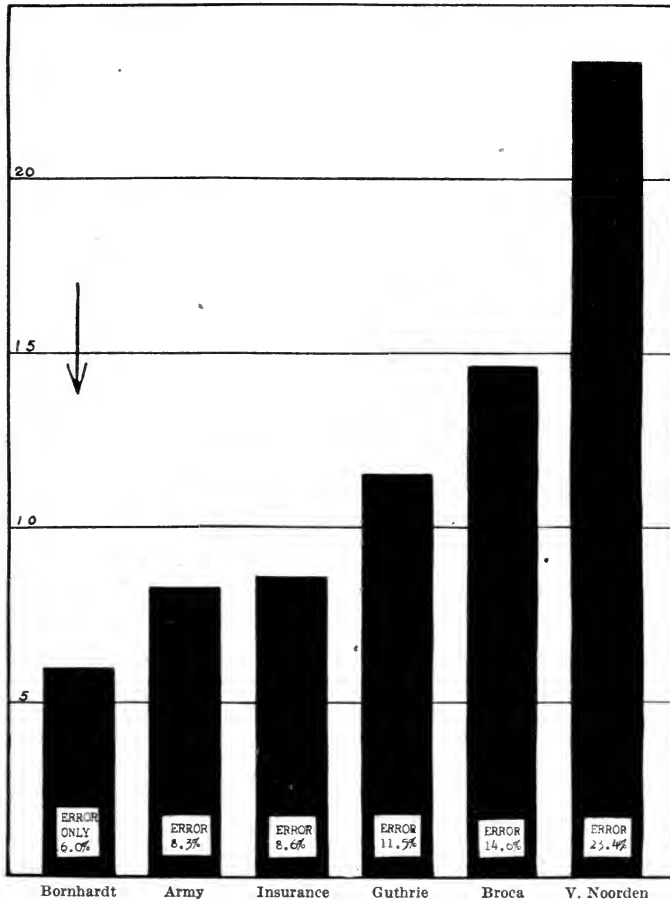
Average error in predicting weight by different standards. Difference between predicted and actual weights, expressed as percentage of the actual weight.

DEFINITIONS

The actual weight is often represented by such terms as: net weight, weight stripped, weight without clothes. This is the criterion by which we are to choose between various standards in the literature.

The Weight of Clothes.—Nearly every standard except the medico-actuarial is expressed as net weight. In our previous observations[5]

men's clothing averaged eight pounds (3.6 kg.), and heels averaged one inch (2.5 cm.). By these values the medico-actuarial table, derived from life insurance records, has been adjusted for net weight in making the comparisons both in the earlier series and the present series. It would have been more accurate, however, for us to have subtracted not 8, but only 6 pounds (2.7 kg.) from the medico-actuarial table to find the predicted weight, because that table was based on weighings with clothes and shoes, but without coat and vest. If, now, we should correct by an increase of 2 pounds our weights predicted by that table, they would be mathematically more correct, but would make no better showing for that standard, since the predictions already run too high. In practice, when using any other than the insurance table, the average weight of house clothes and shoes for men at all ages, sizes, and seasons may be allowed for by Table 2. The figures opposite Quetelet's [6] name were obtained by applying his rule, that clothes average one-eighteenth of the total weight of the male body, to the average weight for the age group here considered, i. e., from 20 to 34 years inclusive (not the average weight for our own group, which is so small relatively and gives 7.8 pounds, i. e., 3.5 kg., but) as computed by us from figures given [9] for 130,301 men insured in the United States and Canada: 152.1 pounds (69.1 kg.) with clothes; then clothes come to 152.1/18 = 8.5 pounds (3.8 kg.).

TABLE 2.—ALLOWANCE FOR MEN'S CLOTHES AND SHOES *

Writer	Weight of Clothes and Shoes	
	Kg.	Lbs.
Fisher and Fisk...	3.1	6.9
Gray..	3.6	8.0
Quetelet..	3.8	8.5
Gaertner[7]...	4.0	8.8
Harris and Benedict[8]....................................	4.0	8.8

* Expressed as kilograms or pounds.

The *ideal weight* is that accompanied by the healthiest or longest life. Too few people are familiar with the insurance experience [3] that one should endeavor to keep his weight at the average for his height and for age 30, the period of full maturity.

6. Quetelet, L. A. J.: Sur l'homme, Paris, 1835, **2**:44, or in the first English translation, A Treatise on Man, Edinburgh, 1842, p. 64.

7. Gaertner, G.: Diätetische Entfettungskuren, Leipzig, 1913, pp. 154, 158, 160; or in English translation, Reducing Weight Comfortably, Philadelphia, 1914, pp. 278, 286, 291.

8. Harris, J. A., and Benedict, F. G.: A Biometric Study of Basal Metabolism in Man, Carnegie Institute, Washington, Publication No. 279, 1919, pp. v, 2, 3, 4, 7, 21, 26, 163, 164, 228.

9. Medico-Actuarial Mortality Investigation, Vol. I, Statistics of Height and Weight of Insured Persons, published by Assn. Life Ins. Directors and Actuarial Soc. of America, N. Y., 1912, pp. 13, 16, 18, 38, 67, 105, 109.

The *average weight,* or usual weight, is the familiar arithmetic mean weight, of subjects grouped by age, height, or other more complex methods. In the medico-actuarial investigation the average weight agreed closely with the central weight (also technically called the mode, the most frequent or the typical weight), thus showing the reliability of using the average.

The *correct weight* may signify either the ideal or the average weight, hence unfortunately it leads to ambiguity.

The *normal weight* also may be interpreted as either the ideal or the average weight. For children Holt [10] says that "the average is not to be confused with the normal. There are considerable variations on either side of the average which should be regarded as within the range of normal. The normal is a zone, not a line." Benedict,[1] too, believes that "for the growing child a gross error has been committed in . . . accepting the average . . . as normal." For adults the insurance committee makes a like statement: "Normal weight for any age and height may vary considerably from the average."

Normal Zone Weight.—This term might be used for the healthy range called "standard lives" by the insurance committee, "the norm of weight" by Gaertner, and more recently emphasized by Holt in the words cited above. The phrase is suitable to express any weight within acceptable limits, but yet not the ideal nor the exact average. The lower boundary of this zone, i. e., the minimal permissible figure beneath which the person is judged underweight, is given by Emerson [11] as 7 per cent., and by Holt as 10 per cent., both for children. For adults, figures which we have calculated from the 1916 printing of the Army standard give 9 per cent. (ranging from 6 to 13 per cent. according to height), and from the 1919 edition 13 per cent. (ranging from 8 per cent. acceptable below the standard weight for 60 inches, up to 19 per cent. below the standard weight for 74 inches); while the insurance companies regarded lives as standard even down to 15 per cent. underweight.

The *standard weight* may mean the ideal, or the average, or the zone.

A *weight standard* is any method, whether table or formula, for predicting weight, as in the title to this paper.

Pathologic Weight, Underweight, Overweight.—Whatever term be used, whatever standard be selected, whatever variation above and beneath the average be accepted as healthy, nearly every writer on obesity or malnutrition starts his reckoning from the predicted weight.

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10. Holt, L. E.: Am. J. Dis. Child. **16**:359 (Dec.) 1918.
11. Emerson, W. R. P.: Am. J. Dis. Child. **17**:251 (April) 1919; Boston M. & S. J. **181**:139 (July 31) 1919.

Predicted weight, calculated weight, estimated weight, expected weight, theoretical weight. This value may be derived from a variety of tables and formulae, of which six are analyzed. It usually corresponds to the average weight.

<div align="center">STANDARDS COMPARED</div>

While the average weight is affected by various factors, e. g., age, sex, country and locality of birth, height, chest-girth, individual variation or sampling; the weight has in nearly every standard offered been considered in connection with one of the following four periods of life: Birth, preschool age, school age, or adult life. The borders of these four groups, except of course the first, vary somewhat according to different writers, but this is of no concern here. For each of the first three age-groups one table was chosen and reproduced in a previous paper;[5] while for the last or adult age group six standards were quoted: Two tables and four formulas. They were Bornhardt's, the Army's, the medico-actuarial, Guthrie's, Broca's and von Noorden's.

Bornhardt's formula was used in the shape given by Fröhlich,[12] Vierordt,[13] Gaertner,[7] Baer,[14] Barker[15] and Vedder,[16] namely: If H be the height without heels in centimeters, C the mean chest girth in centimeters as measured over the nipples, W the net weight in kilograms, then the expected weight for the adult of average constitution is: $W = H \times C/240$.

The Army Table[17] used in our earlier paper[5] has been adhered to in the present study, for the sake of uniformity. The editions of "the physical examination standards . . . are . . . all together seven in number,"[18] from G. O. 66, A. G. O., April 18, 1910, to the latest and larger table authorized Nov. 8, 1918, and published in Washington, 1919. The changes have been slight.

The *Navy Table*[19] gives the same weights for the same heights, i. e., from 64 to 73 inches inclusive, as in the edition of the Army table used here.

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12. Fröhlich, H.: Allgem. medic. Central. Zeitg. **64**:8 (Jan. 2) 1895.

13. Vierordt, H.: Tabellen für Mediziner, Ed. 3, Jena, 1906, p. 97.

14. Baer, J.: Fettsucht (Obesity), in L. Mohr and R. Staehelin's Handbuch der inneren Medicin, Berlin **4**:650, 1912.

15. Barker, L. F.: Clinical Diagnosis of Internal Dis., New York and London **3**:794, 1916; or Monographic Medicine **4**:794, 1916.

16. Vedder, E. B.: Sanitation for Medical Officers, Medical War Manual No. 1, Ed. 2, Philadelphia, 1918, p. 74.

17. McCain, H. P., Adjutant General, War Department, U. S. A. Recruiting Circular No. 2, Washington, Nov. 1, 1916, i. e., G. O. 66 W. D.

18. Hoffmann, F. L.: Army Anthropometry, Prudential Press, Newark, N. J. **34**:46, 1918.

19. Bureau of Navigation, U. S. Navy, Circular Relating to the Enlistment of Men, July 20, 1912, also Circular N. M. S. 126,480, October, 1916; also Manual for the Medical Department, U. S. Navy, 1917, par. 2082.

The *Medico-Actuarial Table* is not reproduced, being very long and available elsewhere.[5, 9, 20]

Broca's Formula, so-called,[15] has also been credited to Quetelet[21] by some,[22] to Allaire[23] and to Robert[24] by others,[7, 25] and cited without credit by still others.[26] We have not succeeded in finding the original, despite search of the supposed sources. The formula is uniformly expressed as: W (in kg.) = H (in cm.) minus 100. Bouchard believes the rule to be approximately true for heights between 168 and 175 cm.; but we find, from applying the rule to the 116 men of our series who fall within this restricted range, that the prediction error, without regard to sign, averages 14 per cent. This is not materially better than the average for our whole series which will be seen in Table 8.

Guthrie's Formula, worked out on patients in Professor Barker's clinic,[15] is: Wt. in pounds = 110 + (5.5 × [ht. in inches minus 60]).

Von Noorden's Formula is given by Barker as: Wt in kg. = ht in cm. × 430 to 480. If from this statement the constant factor for average weight be inferred to correspond to the mean between these two values we get: Wt in kg. = ht in cm. × 455. This interpretation has been applied both in the earlier paper and in this. The results cause regret that we have not been able to see Von Noorden's original statement of his rule.

OBSERVATIONS

The method of recording measurements was as follows: Weight to the nearest half-kilogram (or pound), height and chest-girth to the nearest centimeter, and age to the nearest year.[8, 9, 17, 19, 27] Harris and Benedict[8] point out that "A measurement of stature to the nearest centimeter is about the limit of accuracy. To retain tenths of kilograms is . . . a degree of refinement . . . Finally, when individuals are recorded to the nearest year of age we may remember that they are on the average a quarter of a year older or younger than the age to which they are assigned." Our technic also conformed in many respects to the recommendations of the Committee on Anthropology of the National Research Council.[18] For height a tape 150 by 1.5 cm. (59 x 5/8 in.) was tacked to the wall so that the lower end was 100 cm.

20. Joslin, E. P.: Diabetic Manual, Ed. 2, Philadelphia, 1919, p. 115.

21. Quetelet, L. A. J.: Anthropométrie, Bruxelles, 1871, p. 178, and elsewhere.

22. Sahli, H.: Diagnostic Methods, trans. from German Ed. 5, by N. B. Potter, Ed. 2, Philadelphia, 1911, p. 28. Heckel, F.: Grandes et Petites Obesités, Paris, 1911, p. 105.

23. Allaire: Receuil de mémoires de médecine milit., III e S. **10**:161, 1863.

24. Robert: Receuil de mémoires de médecine milit, III e S. **10**:171, 1863.

25. Fröhlich, H.: Körpergewicht, in Real-Encyclopädie der ges. Heilk., Ed. A. Eulenburg, Vienna, 1887, **11**:199.

26. Bouchard, C.: Traité de Pathologie Générale, Paris, **3**:183, 1900.

27. Treasury Dept., Bureau of War Risk Insurance Form 2A.

above the floor. The subject stood in bare feet, touching the wall with heels, hips, shoulders and head; and a block with square end was pressed down firmly on the scalp. For chest-girth a similar tape was applied on a level with the nipples and read at full inspiration and full expiration; midway between these two readings was taken as the mean chest-girth. The above technic is somewhat more precise than that considered adequate by the Medico-Actuarial Committee:[9] height to the nearest inch. Incidentally, if inches be preferred to centimeters, the inch may well be divided, not into eighths (binary fractions) as in ordinary rules, but into tenths. Similarly, fractions of pounds are better noted as tenths than as sixteenths (ounces). These decimal fractions occupy less space in the chart, are more quickly written down, and are better adapted for averaging and other statistical manipulation, as pointed out by Roberts[28] long ago.

The basal data obtained by our measurements are reported in Table 3, with the subjects arranged according to their actual weights, the lightest first.

METHODS OF STATISTICAL ANALYSIS OR CALCULATIONS

The importance of giving attention to methods considered fussy by some, has been urged by Harris and Benedict in these words: "Data must be . . . interpreted as the statistical constants . . . indicate without any regard to opinions heretofore expressed. In the past, data have been treated almost exclusively by the simple method of averages and graphic representation. . . . By means of the biometric formulas . . . during the past two decades instances of the demonstration of law and order in processes hitherto apparently chaotic have been rapidly multiplying. The reader who is interested in end-results rather than in methods should pass over these features, just as the general biologist must pass over the details of method. . . . in a paper by an organic chemist, realizing that they are essential to the technical development of the subject."

Pearl[29] more recently wrote a paper "to illustrate by a concrete example, not only the importance, but indeed the absolute necessity of mathematical tests of the validity of results and conclusions, if medicine is ever to measure up the standards of scientific logic and accuracy which prevail in some, at least, of the other branches of biologic and physical science. Many, indeed most, of the problems of practical

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28. Roberts, C.: Manual of Anthropometry, London, 1878, p. 26. For example, see Reference 5 in which Table 2 reproduces the American Medical Association's table for children (first published by Crum) with the common fractions translated by us into decimals.

29. Pearl, R.: A Statistical Discussion of the Relative Efficacy of Different Methods of Treating Pneumonia, Arch. Int. Med. **24**:398 (Oct.) 1919.

TABLE 3.—Observed Data

Number	Name	Age at Nearest Birthday, in Years	Height Without Shoes		Chest Girth at Nipple, Mean, in Cm.	Actual Weight, Stripped		
			In.	Cm.		July, 1918, in Lbs.	Jan., 1919. in Lbs.	Per Cent. Gain (+) or Loss (—)
1	2	3	4	5	6	7	8	9
1	P. A. N.	25	60	152	88	105	120	+14
2	J. N. N.	22	66	168	83	107	105	— 2
3	J. M. W.	31	65	165	84	109	120	+10
4	P. J. S.	23	65	165	84	109	136	+25
5	M. L.	24	62	157	80	110	117	+ 6
6	S. S.	25	66	168	82	110	117	+ 6
7	M. K.	22	62	157	83	112	112	0
8	J. K. T.	22	61	155	83	113	126	+12
9	G. W.	30	65	165	89	114	126	+11
10	T. W. S.	23	64	163	88	116	122	+ 5
11	P. C. F.	25	63	160	84	116	124	+ 7
12	A. J. D.	22	62	157	86	116	125	+ 8
13	W. L. D.	28	65	165	86	116	139	+20
14	F. W.	22	64	163	90	117	129	+10
15	J. H. M.	28	63	160	84	118	120	+ 2
16	W. C. W.	28	63	160	89	118	126	+ 7
17	S. A.	27	62	157	85	119	125	+ 5
18	J. S.	26	65	165	88	120	120	0
19	M. J.	24	65	165	90	120	121	+ 1
20	S. Y.	28	64	163	86	121	129	+ 7
21	H. D.	25	68	173	90	121	129	+ 7
22	W. S.	26	58	147	89	122	118	— 3
23	J. P. V.	26	65	165	89	122	122	0
24	J. P. D.	27	63	160	90	122	122	0
25	L. W.	27	64	163	90	122	122	0
26	G. D. W.	33	66	168	80	122	126	+ 3
27	J. J. M.	23	66	168	88	122	133	+ 9
28	A. L. M.	28	71	180	85	122	135	+11
29	J. C. T.	27	66	168	90	123	127	+ 3
30	W. W. W.	27	69	175	90	123	130	+ 6
31	C. O. N.	27	68	173	84	123	137	+11
32	W. J. W.	23	62	157	91	123	140	+14
33	J. F. M.	33	69	175	85	124	129	+ 4
34	M. E. J.	19	69	175	86	124	133	+ 7
35	P. W. E.	26	67	170	81	124	139	+12
36	J. A. F.	24	67	170	88	124	146	+18
37	J. O.	21	65	165	89	125	132	+ 6
38	J. A. W.	25	66	168	93	125	132	+ 6
39	L. S.	22	65	165	90	125	136	+ 9
40	L. C. B.	26	65	165	85	125	144	+15
41	D. E. F.	24	62	157	89	126	128	+ 2
42	L. H. W.	27	66	168	90	126	131	+ 4
43	R. T. F.	23	69	175	89	126	134	+ 6
44	P. S. H.	24	69	175	83	126	137	+ 9
45	A. F. S.	26	65	165	89	128	132	+ 3
46	J. W.	29	68	173	90	128	134	+ 5
47	J. B. R.	23	67	170	80	128	136	+ 6
48	L. L. H.	25	68	173	84	128	141	+10
49	J. K.	23	64	163	86	128	141	+10
50	F. A. C.	30	69	175	90	128	141	+10
51	A. E. B.	31	69	175	86	128	143	+12
52	L. G. M.	23	65	165	88	128	146	+14
53	P. P. L.	32	69	175	85	129	142	+10
54	J. M. D.	23	69	175	85	129	145	+12
55	B. L. F.	23	64	163	89	129	150	+16
56	A. B. R.	28	67	170	91	130	130	0
57	P. J. S.	23	63	160	85	130	131	+ 1
58	R. M.	23	69	175	88	130	135	+ 4
59	O. L. O.	22	63	160	88	130	138	+ 6
60	E. S.	28	66	168	88	130	139	+ 7
61	F. J. F.	30	65	165	88	130	140	+ 8
62	P. R. C.	25	68	173	93	130	150	+15
63	A. B. B.	34	70	178	88	130	154	+18
64	F. S.	24	66	168	86	131	134	+ 2
65	C. M. A.	24	63	160	88	131	135	+ 3
66	V. P. B.	31	71	180	88	131	140	+ 7
67	J. E. J.	26	62	157	90	131	142	+ 8
68	G. F. M.	26	70	178	88	131	144	+10
69	W. S.	22	66	165	90	131	146	+11
70	O. C. M.	25	66	168	84	132	142	+ 8
71	J. F.	29	66	168	86	132	151	+14
72	H. R. S.	21	67	170	87	132	152	+15
73	M. W.	27	68	173	91	133	133	0
74	V. S. D.	29	66	168	86	133	134	+ 1
75	W. D. J.	23	69	175	89	133	135	+ 2
76	F. W. F.	23	67	170	91	133	140	+ 5
77	W. S.	28	65	165	93	133	142	— 7

TABLE 3.—Observed Data—*Continued*

Number	Name	Age at Nearest Birthday, in Years	Height Without Shoes		Chest Girth at Nipple, Mean, in Cm.	Actual Weight, Stripped		
			In.	Cm.		July, 1918, in Lbs.	Jan., 1919. in Lbs.	Per Cent. Gain (+) or Loss (—)
1	2	3	4	5	6	7	8	9
78	W. C. B.	23	68	173	93	133	142	+ 7
79	L. P. A.	26	63	160	91	133	145	+ 9
80	A. B. C.	23	71	180	83	133	150	+13
81	C. L. V.	28	68	173	85	134	144	+ 7
82	M. M.	27	67	170	87	134	145	+ 8
83	L. G.	23	66	168	85	134	148	+10
84	J. L. B.	25	71	180	85	134	148	+10
85	F. M. S.	23	65	165	89	134	152	+13
86	H. W. D.	31	67	170	89	135	133	— 2
87	F. K.	22	68	173	89	135	135	0
88	F. J. D.	27	67	170	89	135	137	+ 2
89	J. M. T.	22	67	170	82	135	139	+ 3
90	M. R. D.	30	64	163	91	135	139	+ 3
91	L. S.	27	66	168	86	135	141	+ 4
92	E. J. C.	32	67	170	91	135	141	+ 4
93	W. J. M.	23	70	178	90	135	148	+10
94	H. A. U.	24	70	178	91	135	148	+10
95	F. N. B.	27	68	173	88	135	150	+11
96	B. J. S.	27	64	163	93	135	150	+11
97	E. H. W.	22	67	170	87	135	152	+13
98	R. O. G.	25	71	180	85	135	153	+13
99	J. S.	30	65	165	88	136	133	— 2
100	J. P. M.	29	67	170	93	136	144	+ 6
101	W. E. W.	28	65	165	88	136	145	+ 7
102	J. A. B.	33	67	170	90	136	149	+10
103	G. S. S.	25	68	173	89	136	152	+12
104	O. E. T.	23	69	175	90	136	152	+12
105	F. J. S.	25	69	175	86	136	153	+13
106	C. J. A.	27	68	173	90	136	156	+15
107	G. D.	28	66	168	89	136	157	+15
108	A. Z.	26	65	165	93	137	148	+ 8
109	S. J. H.	24	69	175	97	137	152	+11
110	J. B.	25	69	175	86	137	161	+18
111	F. J. F.	25	68	173	90	138	121	—12
112	S. J. H.	25	67	170	94	138	139	+ 1
113	J. R. K.	23	67	170	91	138	146	+ 6
114	J. W. B.	23	71	180	85	138	150	+ 9
115	E. S.	25	66	168	94	138	152	+10
116	W. J.	25	66	168	94	138	152	+10
117	C. F. S.	23	68	173	87	138	157	+14
118	E. R. W.	25	68	173	88	139	140	+ 1
119	J. A. A.	25	67	170	89	139	144	+ 4
120	P. H. O.	25	68	173	88	139	146	+ 5
121	J. M. C.	21	72	183	94	139	152	+ 9
122	H. H.	28	68	173	83	140	132	— 6
123	D. K. T.	18	68	173	86	140	137	— 2
124	R. E. M.	24	70	178	91	140	140	0
125	R. E. H.	21	69	175	86	140	145	+ 4
126	A. C. W.	28	70	178	87	140	142	+ 9
127	W. N. S.	26	70	178	88	140	154	+10
128	A. F. S.	28	67	170	92	140	174	+24
129	Z. E. C.	31	72	183	89	141	152	+ 8
130	G. W. K.	24	71	180	91	141	158	+12
131	J. N	24	68	173	90	141	168	+19
132	J. A	28	65	165	91	142	135	— 5
133	C. T.	28	71	180	91	142	142	0
134	P. K.	26	69	175	91	142	144	+ 2
135	H. E. G.	24	63	160	94	142	144	+ 2
136	L. A. M.	21	72	183	90	142	153	+ 8
137	F. R. P.	28	72	183	91	142	153	+ 8
138	M. J. R.	28	68	173	86	143	138	— 3
139	J. S.	27	67	170	90	143	142	— 1
140	W. C. S.	30	66	168	83	143	150	+ 5
141	J. J. L.	22	70	178	91	143	151	+ 6
142	A. W. H.	28	72	183	91	143	152	+ 6
143	P. F.	28	75	191	94	143	155	+ 8
144	L. A .D.	28	71	180	91	143	157	+10
145	G. H. S.	23	64	163	90	144	143	— 1
146	J. W. T.	31	69	175	93	144	144	0
147	K. R.	23	66	168	98	144	156	+ 8
148	W. H. M.	23	71	180	90	144	164	+14
149	J. C. M.	25	71	180	86	144	165	+15
150	V. V.	26	63	160	99	145	146	+ 1
151	L. D. O.	25	70	178	91	145	147	+ 1
152	C. H. F.	23	69	175	90	145	159	+10
153	J. W.	24	69	175	94	145	179	+23
154	W. G. L.	23	67	170	93	146	161	+10

TABLE 3.—Observed Data—*Continued*

Number	Name	Age at Nearest Birth-day, in Years	Height Without Shoes		Chest Girth at Nipple, Mean, in Cm.	Actual Weight, Stripped		
			In.	Cm.		July 1918, in Lbs.	Jan., 1919. in Lbs.	Per Cent. Gain (+) or Loss (—)
1	2	3	4	5	6	7	8	9
155	J. J. K.	26	66	168	93	147	148	+ 1
156	H. W. T.	29	71	180	91	147	157	+ 7
157	C. D. K.	24	71	180	91	147	164	+12
158	J. P. G.	29	66	168	91	148	155	+ 5
159	G. S.	23	67	170	91	148	148	0
160	W. D. L.	26	71	180	91	148	149	+ 1
161	P. J. M.	23	67	170	89	148	157	+ 6
162	M. N. K.	23	69	175	86	148	170	+15
163	G. E. K.	30	67	170	98	148	170	+15
164	J. B. R.	24	69	175	88	148	178	+20
165	R. L. P.	25	70	178	91	149	155	+ 4
166	C. W. S.	25	68	173	89	149	162	+ 9
167	W. S.	25	63	160	94	150	159	+ 6
168	J. S.	30	69	175	95	150	168	+12
169	F. S. W.	25	70	178	94	150	157	+ 5
170	D. L. H.	31	71	180	90	150	157	+ 5
171	C. J. M.	31	68	173	95	150	164	+ 9
172	J. S.	28	70	178	85	150	142	— 5
173	H. O. W.	29	67	170	95	150	169	+13
174	S. W.	28	68	173	94	151	168	+11
175	A. J. S.	26	68	173	95	151	177	+17
176	R. T.	22	62	157	92	152	155	+ 2
177	E. P. A.	29	70	178	94	152	162	+ 7
178	C. A. E.	23	70	178	89	152	165	+ 9
179	H. S. F.	29	70	178	91	152	169	+11
180	H. S.	24	68	173	97	152	169	+11
181	E. E. P.	25	70	178	93	153	165	+ 8
182	F. D. S.	25	70	178	91	153	171	+12
183	L. R.	29	66	168	97	154	170	+10
184	C. M.	22	64	163	97	155	157	+ 1
185	M. A. M.	24	74	188	88	155	159	+ 3
186	H. A. T.	25	68	173	89	155	164	+ 6
187	E. H. B.	28	71	180	90	156	157	+ 1
188	D. W. E.	24	71	180	89	156	160	+ 3
189	T. J. C.	31	64	163	95	156	166	+ 6
190	J. H. C.	31	71	180	98	156	170	+ 9
191	F. S. T.	23	69	175	89	156	171	+10
192	E. A. B.	24	69	175	93	156	176	+13
193	R. M.	28	67	170	96	158	146	— 8
194	D. E. R.	28	70	178	86	158	160	+ 1
195	J. B. M.	27	70	178	95	158	161	+ 2
196	W. B. W.	20	68	173	94	158	165	+ 4
197	J. J. K.	29	68	173	94	158	172	+ 9
198	J. B. O.	29	68	173	99	158	174	+10
199	J. C. T.	28	72	183	85	160	153	— 4
200	R. E. S.	23	68	173	95	160	155	— 3
201	O. H. W.	31	66	168	95	160	175	+ 9
202	W. M. G.	27	69	175	95	160	175	+ 9
203	W. S.	24	71	180	95	161	179	+11
204	J. D. G.	23	72	183	94	161	194	+20
205	E. E. C.	23	69	175	101	162	173	+ 7
206	A. S. S.	28	68	173	84	163	152	— 7
207	W. M. B.	27	73	185	93	163	168	+ 3
208	P. S. K.	25	68	173	98	164	170	+ 4
209	V. P. N.	26	74	188	91	164	183	+12
210	G. J. S.	28	68	173	87	165	162	—18
211	S. P. M.	26	69	175	95	166	183	+10
212	W. F. R.	25	71	180	95	167	168	+ 1
213	T. J. D.	29	69	175	91	167	170	+ 2
214	H. C. L.	27	67	170	95	168	177	+ 5
215	C. E. B.	26	67	170	94	168	179	+ 7
216	A. A. R.	24	67	170	96	169	166	— 2
217	J. K. Z.	28	72	183	101	170	186	+ 9
218	S. E. S.	23	71	180	106	171	183	+ 7
219	W. C. R.	29	70	178	102	172	168	— 2
220	M. W. H.	27	69	175	102	173	173	0
221	I. L.	31	65	165	99	174	180	+ 3
222	E. S.	22	68	173	70	175	162	— 7
223	T. J. D.	29	69	175	99	175	176	+ 1
224	A. L. A.	30	72	183	98	175	190	— 9
225	J. C. M.	25	72	183	95	176	185	+ 5
226	W. F. S.	30	65	165	96	179	184	+ 3
227	F. J. R.	30	71	180	95	180	174	— 3
228	E. E. W.	30	71	180	93	190	185	— 3
229	L. A. T.	24	75	191	102	193	236	+22
	Average	26	67	171	90	141	150	+ 7

medicine in a broad sense are either essentially statistical problems, or their statistical phase is a vitally important one in reaching correct conclusions."

Dreyer,[30] and others,[31] have also recently urged greater care as to the method of collecting and presenting facts.

Prediction Error.—When the weight of an individual is predicted by any method the value may be identical with the observed weight, but in general deviates or errs somewhat from it. This error may be either above or below the actual weight, i. e., either positive or negative in sign; and in consequence it tells us whether the predictions made by a given method are on the whole too large or too small. Since we are in this case testing methods of prediction against actual observation we have taken the differences: calculated weight less actual weight, or $PW - W = D$. This difference D is then reduced from pounds or kilograms to its percentage of the actual weight, plus or minus, i. e., above or below that actual weight; or

$$\frac{(PW - W)\ 100}{W} = \frac{100\ D}{W} = \% $$

prediction error $= E$. This percentage prediction error is our common unit on which all further discussion is based hereafter. For example, in Table 4, Bornhardt's method applied to Case 1 gives: $PW = 55.9$ kg. (123 pounds), $W = 47.7$ kg. (105 pounds), hence $D = 8.2$ kg. (18 pounds), from which by substitution in the above formula we find the prediction error is $8.2/47.7 = 17$ per cent., or $18/105 = 17$ per cent. In other words, this value E will be the same no matter whether our observed data have been recorded in metric or customary units, though ordinarily of course all one's data are recorded in the same unit. The error for each individual has been calculated only to the nearest integral, while the average error for each standard is given to about 1 per cent.

The reasons for this percentile manner of expression are:

. 1. When comparing the varying errors obtained by applying the same formula to the 229 different subjects, percentage errors are always comparable, whereas kilogram or pound errors are often not comparable owing to the subjects' varying weights.

2. When comparing the average of these 229 errors by one formula with the average of the errors by a second formula on the same 229 cases, percentage errors are always comparable, whereas kilogram or pound errors are often not comparable because the two formulas are expressed in different units: one metric, the second English.

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30. Dreyer, G., and Walker, E. W. A.: Iatro-mathematics, in Contributions to Medical and Biological Research, Dedicated to Sir William Osler, New York, **1**:40, 1919.

31. Editorial, J. A. M. A. **73**:1531 (Nov. 15) 1919; also, **Kilgore, E. S.:** J. A. M. A. **75**:86 (July 10) 1920.

3. Furthermore, as will be clearer further on, the expression of the errors as percentages automatically determines limits of the class intervals convenient for tabulating the frequency of each of the different sized errors, for reckoning the average of the 229 errors, or their standard-deviation, or their coefficient of variation.

Analysis of the error, to determine the relative precision of prediction by different methods, is carried out by the application of the following criteria or constants:

1. The frequency distribution of error.

2. The average error with regard to sign, i. e., the algebraic mean.

3. The average error without regard to sign, i. e., the arithmetical mean.

4. The standard error, i. e., the square root of the sum of the squares of the errors.

5. The range between the maximum error and the minimum error.

6. The standard deviation of the average error, i. e., the square root of the sum of the squares of the deviations of each of the 229 errors from the average error.

7. The coefficient of variation.

The next step is to summarize the errors in the predictions by each method, as given in Table 4, into a frequency-distribution table, Table 5, in conformity with the dictum: "In all cases of published work the figures of the frequency-distribution should be given; they are absolutely fundamental." [32]

Calculation of the Mean Error.—Method I (Yule [32]): From frequency distribution Table 5.

Let A = an arbitrary value or guess at approximate mean.

Let M = true mean.

Let d = difference between approximate and the true mean = M-A = Sum f. z/N.

Then by substitution of figures from Table 5.

$$d = \frac{\text{Sum (f.z)}}{N} = \frac{+453 - 452}{229} = \frac{+1}{229} = 0.0044 \text{ class-intervals.}$$

Now in making the frequency Table 5, each class-interval was taken as = 1 per cent. error.

$$\therefore d = 0.0044 \text{ per cent.}$$
$$M = A + d = 6 + 0.0044 = 6.0044 \text{ per cent.}$$

Method II (Harris and Benedict): From basal Table 3.

$$M = \frac{\text{Sum E}}{N} = \frac{1374}{229} = 6.00 \text{ per cent.}$$

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32. Yule, G. U.: Introduction to the Theory of Statistics, Ed. 5, London, 1919, pp. 79, 112, 133, 141, 144, 153.

TABLE 4.—Method of Computing Prediction Error; with Examples from the Application of Bornhardt's Standard to the Series of 229 Males

	Case Number	Prediction (Standard: Bornhardt's Formula)			
		Predicted Weight	Difference of Predicted Weight from Actual Weight, Too High (+) Too Low (−)	Percentile Prediction Error, Prediction Error, or Simply Error	Error Squared
		PW	PW − W = D	$\dfrac{D}{W} = E$	E^2
		Kg. or Lbs.	Kg. or Lbs.	Per Cent. of Actual Weight W	
	1	55.9	+ 8.2	+17	289
	2	127	+20	+19	361
	-- -- --	-- -- -- --	-- -- -- -- --	-- -- -- -- --	-- -- -- --
	229	179	−14	− 7	49
Arithmetic sum............				1,374	14,283
Mean error.................				6.0%	62.37
Root-mean-square-error..					7.89%
Range of error.............			0 to +20 and −64 lbs.	0 to +19 and −36%	0 to 1,296
Standard deviation........				5.14%	

TABLE 5.—Summary of Prediction Errors in Column E of Original Table 4, to Show Frequency-Distribution, Average Error and Standard-Deviation. Standard: Bornhardt's. Series: 229 Soldiers

1	2	3	4	5	6
Percentage Prediction Error	Frequency	Deviation from Arbitrary Value A	Product Column 2 × Column 3	Deviation Squared	Product Column 2 × Column 5
E	f	z	f.z	z^2	$f.z^2$
0	9	− 6	− 54	36	324
1	33	− 5	−165	25	825
2	27	− 4	−108	16	432
3	25	− 3	− 75	9	225
4	16	− 2	− 32	4	64
5	18	− 1	− 18	1	18
			−452		
6	24	0		1	8
7	8	1	8	4	44
8	11	2	22	9	45
9	5	3	15	16	112
10	7	4	28	25	300
11	12	5	60	36	252
12	7	6	42	49	294
13	6	7	42	64	256
14	4	8	32	81	405
15	5	9	45	100	100
16	1	10	10	121	484
17	4	11	44	144	432
18	3	12	36	169	507
19	3	13	39	900	900
36	1	30	30		
			+453		
Sum............	229	....	+1	...	6,027
Mean..........	...	....	+0.0044	...	26.3

Calculation of the Standard Deviation.

Method I (Yule): From the frequency distribution Table 5.

$$S. D. = \sqrt{\frac{Sum\ f.z^2}{N} - d^2}$$

$$= \sqrt{\frac{6027}{229} - (0.0044)^2}$$

$$= \sqrt{26.3 - 0.000019}$$

$$= \sqrt{26.299981}$$

$$= \sqrt{26.3}$$

$$= \quad 5.13\%$$

Method II (Harris and Benedict[28]): From Tables 3 and 4.

$$S. D. = \sqrt{\frac{Sum\ E^2}{N} - \left[\frac{Sum\ E}{N}\right]^2}$$

$$= \sqrt{\frac{Sum\ E^2}{N} - (M)^2}$$

$$= \sqrt{\frac{14283}{229} - (6.00)^2}$$

$$= \sqrt{62.37 - 36.00}$$

$$= \sqrt{26.37}$$

$$= \quad 5.14\%$$

Average Error with Regard to Sign, Algebraic Mean.—When a given prediction method gives results which are on the average too high, the mean error with regard to sign will have the positive sign.[5] When it is too low, it will have the negative sign. Dividing the sum of the errors with regard to sign by the total number of individuals in the series in hand we have a measure of the average error in the direction of too high or too low prediction. This value is given in Tables 7, 8, 9. It is liable to give a factitious appearance of accuracy because the plus and minus errors tend to cancel, and the algebraic mean is therefore only mentioned in passing, while great attention is given to the arithmetic mean discussed below. Before passing to that however, another measure of the direction of the error may be presented in Table 6.

TABLE 6.—PREDICTION ERROR TOO HIGH OR TOO LOW

	Number of Times				Percentage of Times			
	Too Low	Too High	Cor-rect	Total	Too Low	Too High	Cor-rect	Total
Bornhardt's	89	131	9	229	39	57	4	100
Army	82	111	9	202	41	55	4	100
Medico-Actuarial	79	144	5	225	35	63	2	100
Guthrie's	46	175	8	229	20	76	4	100
Broca's	27	201	1	229	12	87	1	100
von Noorden's	4	223	2	229	2	97	1	100

Average Error Without Regard to Sign, Arithmetic Mean.—But the question, however, as to whether a given prediction method yields on the whole too high or too low values is not the only one to be answered. One wishes to know the extent of errors, either above or below the actual weight, in the case of each of the methods used. This

extent may be reckoned (1) by ignoring the signs and simply regarding a difference between observed and predicted body weight as an error of a given magnitude in kilograms, or better as an error of the equivalent percentage of the actual weight; then dividing the sum of these errors by the number of individuals in the series, the formula is: Sum E/N = M. Another method (2) for obtaining the mean, useful as a confirmation of the above briefer method, is seen in Table 5.

This mean error sometimes proves identical for two methods under comparison, so that further analysis by other constants is necessary. Furthermore, these other constants may be of service even in cases where they are not made absolutely necessary by similarity of means. For the arithmetical mean has two disadvantages.[8] First, it does violence to sound mathematical usage with regard to signs. Second, it gives errors importance only proportional to their magnitudes, while one may consider, in a comparative test like the present, that very great errors should be given proportionally more weight than very slight deviations. Both of these drawbacks may be avoided by figuring the standard error.

Standard Error, or Root-Mean-Square Error.—In this paper this term is used in another sense than that usual among statisticians. Here, the above mentioned magnitudes of the deviations or of the percent errors may be logically weighted and the transgression against the law of signs avoided by squaring the errors, summing the squares, obtaining their mean and extracting its squares.

Range.—The error made by Bornhardt's or any other method is of course variable, and for this variation, technically called dispersion, "the simplest possible measure . . . is the actual *range,* i. e., the difference between the greatest and least values observed. While this is frequently quoted, it is as a rule the worst of all possible measures for any serious purpose." [32] A better measure is the standard deviation, and better still, the coefficient of variation.

Standard Deviation.—Yule[32] states that "The standard deviation should always be used as the measure of dispersion, unless there is some very definite reason for preferring another measure, just as the arithmetic mean should be used as the measure of position." The standard deviation is the square root of the average of the squares of all deviations as measured from the arithmetic mean of the observations; and therefore is called the root-mean-square deviation from the mean. To square all the deviations may seem artificial, but such root-mean-square quantities frequently occur in other branches of science. The computation may be made either from the frequency Table 5, modeled on Yule, or from the briefer formula of Harris applied to figures in Table 4.[8, 33]

33. Harris, J. A.: Am. Naturalist **44**:693, 1910.

Coefficient of Variation.—Standard deviations are not comparable when the respective means are of different size, hence the need of translating the former from absolute to percentage values, thus securing the coefficients of variation. The formula is 100 S.D./M. = C. V.

DATA COMPUTED AND ANALYZED

Error in Relation to the Six Standards.—Our findings are summarized for the first series in Table 7, for the second or present group in Table 8, and for the two groups consolidated in Table 9. In each table note the lower values across the first row, as compared with successive rows down the page.

TABLE 7.—Error in Relation to Standards. Summary of Prediction Errors Computed from Original of Table 4. Standards: All Six. Series: Twenty Males

Rank in Order of Accuracy	Standards Compared	Number of Subjects	Average or Mean Error		Root-Mean-Square Error or Standard Error	Standard-Deviation of Mean Error	Coefficient of Variation of Mean Error
			Sum E / N				
			Algebraic Mean	Arithmetic Mean	$\sqrt{\dfrac{Sum\ (E^2)}{N}}$	$\sqrt{\dfrac{Sum\ (E^2)}{N} - M^2}$	100 SD / M
			Average With Regard to Sign	Average Without Regard to Sign			
		N	A	M	S.E.	S.D.	C.V.
1	2	3	4	5	6	7	8
1	Bornhardt's.....	20	− 2.7	5.6 ± 0.542	6.6	3.6	64.3
2	Army............	18	+ 2.6	7.3 ± 1.03	9.8	6.5	89.0
3	Medico-Actuarial............	20	+ 3.1	7.4 ± 0.77	8.9	5.1	68.9
4	Guthrie's........	20	+ 8.8	9.5 ± 1.22	12.5	8.1	85.3
5	Broca's.........	20	+13.1	13.1 ± 1.37	15.9	9.1	69.5
6	v. Noorden's....	20	+19.8	19.9 ± 1.84	23.4	12.2	61.3

TABLE 8.—Error in Relation to Standards. Standards: All Six. Series: 229 Soldiers

Rank in Order of Merit	Standards Compared	Number of Cases	Average or Mean Error		Standard Error	Standard Deviation	Coefficient of Variation
		N	A	M	S.E.	S.D.	C.V.
1	Bornhardt's..........	229	+ 1.4	6.0 ± 0.228	7.9	5.1	85.0
2	Army.................	202	+ 2.0	8.4 ± 0.318	10.7	6.7	79.6
3	Medico-Actuarial......	228	+ 3.5	8.7 ± 0.291	10.9	6.5	74.7
4	Guthrie's.............	229	+ 8.7	11.7 ± 0.374	14.4	8.4	71.8
5	Broca's...............	229	+13.0	14.7 ± 0.418	17.4	9.4	64.0
6	v. Noorden's..........	229	+23.6	23.7 ± 0.504	26.3	11.3	47.7

Error in Relation to Age.—The question may be raised, do prediction errors vary proportionately with age, actual weight, height, or chest-girth (either directly, inversely, or at the extremes from the average)? The age ranged from 18 to 34 years, with an average of

25.9 years. The mode, i. e., the most frequent or typical age, was 23 years. Eighty-six per cent. of the men were in their twenties. Ninety per cent. were 23 or over, "the age when the average man has attained his full stature and bulk," according to Quetelet,[6] Dawson, Aitkin and Beddoe.[21] It should be remembered that this age is taken from the nearest, not the last, birthday. The frequency distribution shows that the error is least at the average age, i. e., 26, runs high at isolated ages, but does not tend to be greater over the younger or indeed over any significant period. The errors for the extreme age groups are bracketed, as being unreliable, owing to the small number of cases in each of those classes (Table 10).

TABLE 9.—Error in Relation to Standards.
Series: 20 + 229 = 249 Males

Rank in Order of Merit	Standards Compared	Number of Subjects	Average or Mean Error		Standard Error	Standard Deviation	Coefficient of Variation
		N	A	M	S.E.	S.D.	C.V.
1	Bornhardt's..........	249	+ 1.1	6.0 ± 0.213	7.8	5.0	83.3
2	Army..............	220	+ 2.0	8.3 ± 0.304	10.7	6.7	80.7
3	Medico-Actuarial......	248	+ 3.5	8.6 ± 0.274	10.7	6.4	74.4
4	Guthrie's.............	249	+ 8.7	11.5 ± 0.358	14.3	8.4	73.0
5	Broca's..............	249	+13.0	14.6 ± 0.396	17.3	9.3	63.7
6	v. Noorden's.........	249	+23.2	23.4 ± 0.485	26.0	11.4	48.7

TABLE 10.—Distribution of Error According to Age
Standard: Bornhardt's.   Series: 229 Males

		18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	Sum
	Nearest Age																		
Class-frequencies, i. e., number of cases in each class...........		1	1	1	5	15	38	23	31	19	20	30	15	12	12	2	3	1	229
Average error at each age........		(2	11	6	6)	9	5	5	6	4	6	7	5	9	7	(6	5	11)	

Error in Relation to Actual Weight.—The weight varied from 47.6-87.5 kg. (105-193 lbs.), with a mean of 64.1 kg. (141 lbs.), and a mode of 61.2 kg. (135 lbs.). The frequency distribution is summarized in Table 11. In choosing the magnitude of the class-interval, the frequency distribution unit of 1 pound each would have given 88 classes which would have been unwieldy and would have included too few figures in each class; units of one kilogram each with 40 classes, would have the same drawbacks; 2 kilogram intervals would have given the very desirable number of classes,[32] but would still have had a rather small number of cases in each. The size chosen also has the advantage of keeping both kilos and pounds as integers. Even with only eight classes the last covers only two cases, and must be ignored in the inter-

pretation. The error is seen to be least for the groups including the central weights, as would be expected, and to increase toward the extremes.

Error in Relation to Height.—The stature in bare feet averaged 171 cm. (67 inches), ranging from 147-191 cm. (58-75 inches). No correlation is seen in Table 12.

TABLE 11.—DISTRIBUTION OF ERROR ACCORDING TO WEIGHT *
STANDARD: BORNHARDT'S. SERIES: 229 MALES

Weight	Kg.	48 and under 53	53—	58—	63—	68—	73—	78—	83—	47.6-87.5
	Lbs.	106 up	117—	128—	139—	150—	161—	172—	183—	105-193
Number of cases.........		13	31	73	49	36	16	9	2	229
Average error for each weight class............		12	9	5	4	5	7	13	(13)	

* Each class-interval = 5 kg. = 11 lbs.

TABLE 12.—DISTRIBUTION OF ERROR ACCORDING TO HEIGHT *
STANDARD: BORNHARDT'S. SERIES: 229 MALES

Height	Cm.	147 and under 152	152—	157—	162—	167—	172—	177—	182—	187—	147-191
	In.	58 up	60—	62—	64—	66—	68—	70—	72—	74—	58-75
No. of cases......		1	2	19	33	51	65	43	11	4	229
Average error for each class..		(2	11)	5	8	5	6	5	6	(7)	

* Each class interval = 5 cm. = 2 inches.

TABLE 13.—DISTRIBUTION OF ERROR ACCORDING TO CHEST-GIRTH *
STANDARD: BORNHARDT'S. SERIES: 229 SOLDIERS

Chest girth	Cm.	70	79 and under 81.5	81.5—	84—	86.5—	89—	91.5—	94—	96.5—	99—	101.5—	104—	70-106
	In.	28	31 up	32—	33—	34—	35—	36—	37—	38—	39—	40—	41—	28-42
No. of cases......		1	4	9	40	29	79	15	33	9	6	3	1	229
Average error for each class..		36	3	8	6	5	6	7	6	5	4	5	2	

* Class interval = 2.5 cm. = 1 inch.

Error in Relation to Chest-Girth.—The perimeter of the thorax, at the level of the mammillae, midway between inspiration and expiration, varied from 70 to 106 cm. (from 28 to 42 inches) with an average of 90 cm. (35 inches). No correlation is evident (Table 13).

CONCLUSIONS

The normal weight for an American man may be predicted somewhat more accurately by Bornhardt's formula than by the Army and Navy table, the Medico-Actuarial, Guthrie's, Broca's, or Von Noorden's standard. This was true for a series of 249 native-born men, aged 18 to 34 years, inclusive. Whether it would also hold true for other men, for women and for children, we cannot state. Bornhardt's standard did not vary in accuracy at varying ages, weights, heights and chest-girths. Though other writers have urged the value of routinely recording the chest perimeter as well as height, nobody has incorporated it into a formula as simple as Bornhardt's. And, just as his rule (based on height and chest-girth) as a rough measure of surface seems both theoretically and empirically the best guide so far offered for guessing weight, so we expect that experiment would discover an even better rule (based on height, chest and a third factor) expressing a rough measure of volume. For fundamentally weight must be proportional, not to length nor surface, but to cubic mass.

BUNDLE BRANCH BLOCK AND ARBORIZATION BLOCK *

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ST. LOUIS

For the first few years after the introduction of the string gal-
nometer into clinical medicine, electrocardiographers devoted most
their attention to the analysis of the cardiac irregularies. This field
s been so extensively cultivated that it is approaching exhaustion,
d there is an increasing tendency to turn to the significance of abnor-
ilities of the form of the electrocardiographic deflections as a subject
research. The notable contributions which have recently been made
this subject, and the confusion that must result from the conflicting
ews that have lately been expressed, make it seem advisable to sum
, in a critical way, the present state of our knowledge. The present
ticle is devoted to a careful digest of the literature on those abnor-
ilities of the ventricular complex which indicate disturbances of
raventricular conductivity, and to the presentation of a number of
iginal observations which have a bearing on their interpretation.

EARLY WORK ON BUNDLE BRANCH BLOCK

Our knowledge of the changes in the form of the ventricular com-
ex which result from lesions of the two chief divisions of the His
ndle dates from the work of Eppinger and Rothberger.[1] These
thors made a large number of experiments on dogs in which they
jected solutions of silver nitrate into the ventricular muscle with the
idea of determining the effect of destroying various portions of the
muscle of these chambers on the electrocardiogram. They found that
in many instances a comparatively large mass of muscle might be
injured without changing the form of the electrocardiogram, while in
other experiments relatively small lesions produced very striking
results. They were struck by the effectiveness of injections into the
interventricular septum in comparison with those made into the free
walls of the ventricles, and they suspected that this was due to injuries
of the larger branches of the conducting system which lie beneath the
septal endocardium. In a second series of experiments [2] they confined

their attention to these special tissues, and by introducing a small knife through the ventricular wall they were able to sever the chief right and left branches of the His bundle. Remarkable changes in the form of the electrocardiogram resulted. A single lead from esophagus to rectum was used. When the right branch was cut, the normal, relatively small, physiologic ventricular complexes gave place to diphasic complexes of large amplitude closely resembling the ventricular complexes obtained by electrical stimulation of the surface of the left ventricle. The initial phase (QRS) was downwardly directed and was of greatly increased duration; it was immediately followed by a large upwardly directed final deflection, an exaggerated T. Section of the left branch produced similar results, except that the direction of both phases was reversed so that the complexes resembled those obtained by stimulation of the surface of the right ventricle.

While these experiments were in progress, the authors were on the lookout for clinical cases showing electrocardiographic abnormalities similar to those that they had produced experimentally, and Eppinger and Stoerk [3] were fortunate in discovering five such cases. Two of these patients died while in hospital and necropsies were obtained. Both had been observed over long periods and had constantly shown abnormal ventricular complexes of a definite type. These complexes were typically diphasic in all leads; both phases were of large amplitude in Leads I and III, and the QRS interval was much greater than normal. The first phase (QRS) was upwardly directed in Lead I and downwardly directed in Leads II and III. Since Leads II and III corresponded more closely to the esophageal-anal lead used in the previously mentioned experiments than did Lead I, the authors made the diagnosis of right bundle branch block in each case. At the necropsies very careful macroscopic and microscopic examinations of the branches of the His bundle were made and in both instances lesions were found completely transecting the right branch while the left branch was normal. These pathologic findings are of the greatest importance for, so far as we know, they are the only ones of their kind on record. They demonstrate that lesions that transect the right branch of the His bundle in man produce diphasic ventricular complexes of which the first phase (QRS) is upwardly directed in Lead I, and downwardly directed in Lead III. The conclusion arrived at by Fahr [4] from theoretic considerations that what we are accustomed to call right bundle branch block is really left bundle branch block is not in accord with these facts.

3. Eppinger, H., and Stoerk, O.: Zur Klinik des Elektrokardiograms, Ztschr. f. klin. Med. **71**:157, 1910.

4. Fahr, G.: An Analysis of the Spread of the Excitation Wave in the Human Ventricle, Arch. Int. Med. **25**:146 (Feb.) 1920.

The criteria to be used in recognizing bundle branch block were not very clearly stated by Eppinger and his collaborators. Carter,[5] working in Lewis' laboratory, published a large series of curves in 1911 which he interpreted as examples of the bundle branch block, and gave a table contrasting the features of the normal and the abberrant ventricular complex.

Normal	Abberrant
1. Supraventricular complex. Presence of auricular or P summits.	1. Supraventricular complex. Presence of auricular or P summits.
2. P-R interval 0.13 to 0.18 second, never more than 0.2 second.	2. P-R interval frequently prolonged beyond 0.2 second.
3. QRS interval less than 0.1 second and less than one-third of entire complex.	3. QRS interval exceeds 0.1 second and as a rule constitutes more than one-third of entire complex.
4. Relatively small amplitude of initial deflections.	4. Relatively increased amplitude of initial deflections.
5. Final deflection T upright and in the same direction as the most prominent deflection (R) in Leads I and II, and usually in Lead III.	5. Final deflection T' usually in a direction opposite to that of the prominent initial deflection.
6. Initial deflections, as a rule unnotched.	6. Initial deflections almost always show notching in one lead at least. Many bizarre forms seen.
7. Final deflection T as a rule plainly to be seen, but not exaggerated.	7. Final deflection T' frequently much exaggerated.

Not all of the curves published by Carter as examples of bundle branch block show all the abnormalities catalogued in the second column of the table; many are not of particularly large amplitude; others do not show a QRS interval greater than 0.1 second. All, however, are diphasic in Leads I and III. Two cases, one in which the abberrant electrocardiograms were transitory and one in which they developed while the patient was under observation, are of unusual interest. The first illustrates the contrast between curves indicating left ventricular preponderance and those indicating right bundle branch block and the second illustrates the contrast between the abberrant curves and electrocardiograms of relatively normal outline from the same individual. In none of Carter's cases were necropsies reported.

Cohn and Lewis,[6] however, reported the pathologic findings in four cases of supposed bundle branch block from the same laboratory. In none of these cases could the electrocardiographic diagnosis be substantiated. In commenting on the discrepancy between the electrocardiographic and pathologic findings, the authors point out that the functional changes shown by electrocardiograms do not necessarily rest on recognizable pathologic lesions.

5. Clinical Observations on Defective Conduction in the Branches of the A-V Bundle, Arch. Int. Med. **13**:803 (July) 1914.

6. Cohn, A., and Lewis, T.: The Pathology of Bundle Branch Lesions of the Heart, Proc. New York Path. Soc. **14**:207, 1914.

Further clinical examples of bundle branch block have been reported by Mathewson [7] and others; frequent examples are seen at every clinic where large numbers of patients with heart disease are studied electrocardiographically. It is notable that right bundle branch block is very much more common than left bundle branch block, and this has been attributed to the difference in the character of the two branches. The right branch passes to the chief papillary muscle of the right ventricle as a single strand while the left branch subdivides almost at once spreading out into a broad fan so that it can hardly be completely divided, except by a relatively large lesion.

LATER WORK ON BUNDLE BRANCH BLOCK

Following certain criticisms of the work of Eppinger and his collaborators, Rothberger and Winterberg [8] repeated the experimental work of Eppinger and Rothberger, using in this instance the ordinary three leads. They found that when one of the chief branches of the His bundle was severed, typical diphasic complexes resulted, but the initial deflections (QRS) in Leads I and III had the same and not opposite directions as in the human cases reported by Eppinger and Stoerk.

In the course of his work on the spread of the excitatory process over the heart, Lewis [9] found it necessary to reinvestigate this subject. He found that in the majority of dogs the initial phases of the curves obtained by section of the right branch were downwardly directed in all leads. He termed curves of this type concordant. In a small percentage of dogs QRS of Lead I was upwardly directed as in right bundle branch block in man. These curves were termed discordant. Section of the left branch always gave curves of the concordant type; QRS was upwardly directed and T downwardly directed in all leads. Why should right bundle branch block produce concordant curves in most dogs and discordant curves in man? Lewis gives evidence to show that it is not due to a difference in the position of the heart with reference to the leads used nor to other similar factors. The discordant curves obtained from a small percentage of dogs furnish the solution; the cause is to be found in the heart itself. Lewis observed that he could predict from the form of the physiologic electrocardio-

7. Mathewson, G. D.: Lesions of the Branches of the Auriculo-Ventricular Bundle, Heart **4**:385, 1913.

8. Rothberger, C. J., and Winterberg, H.: Zur Diagnose der einseitigen Blockierung in den Tawaraschen Schenkeln, Zentralbl. f. Herz u. Gefässkr. **5**:206, 1913.

9. Lewis, T.: The Spread of the Excitatory Process in the Vertebrate Heart, Phil. Tr. Roy. Soc. Lond. **207**:221, 1916.

gram of a given animal which type of curve would result from section of the right branch of the bundle. When R1 (R of Lead I) was of small amplitude, concordant curves resulted, and when R1 was of large amplitude, discordant curves were produced. An inspection of the hearts from which discordant curves were obtained showed that there was less bridging of the cavity of the left ventricle by subdivisions of the left branch than in hearts which gave concordant curves. Lewis, therefore, attributes the difference between the curves of bundle branch block in the dog and the curves of similar lesions in man to greater bridging of the ventricular cavities in the former by strands of special conducting tissue. The experiment performed by Lewis on a Rhesus monkey indicates that in this animal the curves of bundle branch block are of the discordant type, as in man.

ANALYSIS OF THE FORM OF THE VENTRICULAR COMPLEX IN BUNDLE BRANCH BLOCK

The analysis of the ventricular complex in bundle branch block and the analysis of the normal ventricular complex are very closely related and will be discussed together. In each case the analysis depends on a knowledge of the course of the excitation wave over the ventricular muscle. From the auricles the normal impulse passes down the His bundle and its chief branches, through the larger and smaller sub-divisions of these branches, into the Purkinje network which lines both ventricles.[10] From the Purkinje network, which does not penetrate the ordinary muscle deeply, the impulse passes into the muscle of the ventricular walls. The rate of travel through the Purkinje tissue is about ten times the rate through the ordinary ventricular muscle (the figures are, from 3,000 to 5,000 mm. per second for the former and from 300 to 500 mm. per second for the latter). As a result of its much greater speed of travel through the conducting system, and the failure of this system to penetrate the ordinary muscle deeply, the excitation wave spreads over the endocardial surface very quickly and its average course through the ventricular walls is roughly perpendicular to the endocardial surface (Fig. 1). When, as in man, there is little or no bridging of the ventricular cavity by special conducting tissue, the excitation wave spreads down the Purkinje network of the septum toward the apex and thence upward through the network of the free walls; the subendocardial muscle of these regions is activated in the same order. Because of its relatively slow rate of progress through the ordinary muscle, however, the time of arrival of the excitatory process at a point on the epicardial surface of the ventricles is largely

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10. Lewis, T., and Rothschild, M. A.: The Excitatory Process in the Dog's Heart. Part II, The Ventricles, Phil. Tr. Roy. Soc. Lond. **206**:181, 1915.

controlled by the thickness of the muscle at that point. The course of the excitation wave over the ventricular muscle is diagrammatically shown in Figure 1, which also shows the relationship of the direction in which various regions are activated to the equilateral triangle of Einthoven. It was shown by Lewis and his collaborators that the time taken by the impulse to complete its course through the ventricular muscle was equal to the QRS interval and that the deflections which comprise the QRS group are produced by the activation of the ventricles.
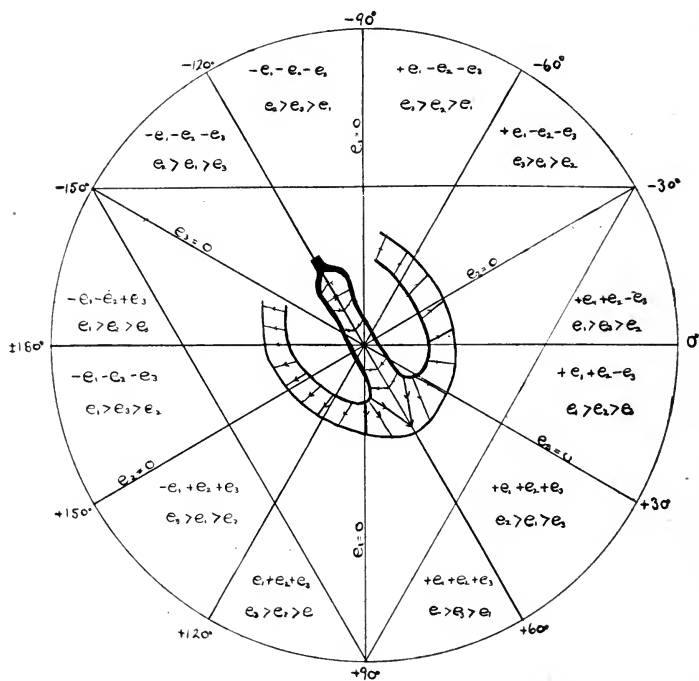
Fig. 1.—Diagrammatic representation of the course of the excitation wave over the ventricular muscle. The direction of the excitation wave through the ventricular walls is shown by arrows. The relationship of the course of the excitation wave through the ventricular walls to the equilateral triangle of Einthoven is shown. e1 equals deflection in Lead I, e2 equals deflection in Lead II, e3 equals deflection in Lead III. See text and compare with Figure 6.

It was shown also [10] that section of the right branch of the His bundle caused a great delay in the spread of the excitation wave over the muscle of the right ventricle; the activation of the left ventricle was not disturbed. This delay is due to the absence of any connecting link between the conducting networks of the two ventricles below the main stem of the His bundle, so that when the right branch is cut, the excitatory impulse can only reach the right ventricular Purkinje system

by passing through the ordinary muscle of the ventricular septum. It is mainly the slow speed of travel through the septum that causes the great QRS interval of bundle branch block. Since section of the right branch of the His bundle delays the activation of the right ventricle but does not disturb the activation of the left ventricle, the first part of the QRS group of right bundle branch block curves is an expression of pure left ventricular effects (levogram). Similarly, the first part of the QRS group of left bundle block curves is an expression of pure right ventricular effects (dextrogram). By clamping first the right and then the left branch in a dog Lewis [9] was able to obtain both levogram and dextrogram, as well as the physiologic electrocardiogram, from the same animal. Synchronous points on these curves were obtained by a method which need not be described here. It was then found that by algebraic summation of the levogram and dextrogram the normal QRS group could be reproduced. The extraordinarily close resemblance of the calculated to the recorded normal QRS in this experiment proves that the normal QRS group is a summation of right and left ventricular effects, and that these effects can be obtained separately by producing bundle branch block first on one side and then on the other.

In the monkey and in man the dextrogram usually begins with a slight upward deflection (R') in Lead I and a small downward deflection (Q') in Lead III. The main deflection is downwardly directed (S') in Lead I and upwardly directed (R') in Lead III. The levogram is similar in form, but the main deflection is upward in Lead I (R') and downward in Lead III (S'), and the preliminary deflections (Q'1 and R'3) are also oppositely directed to the preliminary deflections of the dextrogram in the same leads. It is apparent, therefore, that the constitution of the normal QRS group of man is as follows; Q 1 (Q of Lead I) is a left, and Q 3 a right ventricular effect; R 1 is mainly a left, and R 3 mainly a right ventricular effect; S 1 is a right, and S 3 a left ventricular effect (Lewis [9]).

ELECTRICAL EFFECTS PRODUCED BY THE ACTIVATION OF A SIMPLE
MUSCLE AND THEIR RELATIONSHIP TO THE INTERPRETATION
OF THE NORMAL AND ABNORMAL VENTRICULAR
COMPLEX

From a theoretical consideration of the electrical effects produced by the activation of simple muscles, Fahr [4] reached conclusions which are not in accord with Lewis' analysis of the normal electrocardiogram, to which we have adhered in this paper, and which have led him to believe that the abnormal ventricular complexes which are at present regarded as evidence of right bundle branch block are really due to

left bundle branch block. Before proceeding with the analysis of the curves of bundle branch block, it is necessary to examine this subject in some detail.

Let A-B (Fig. 2) represent a simple strip of heart muscle immersed in a conducting medium to which the galvanometer terminals are attached in such a way that relative negativity at R will cause an upward and relative negativity at S a downward deflection in the completed electrogram.

The muscle A-B is asymetrically placed with reference to the ends of the container R and S at which the electrodes are attached. Will the asymmetric position of the muscle influence the form of the elec-
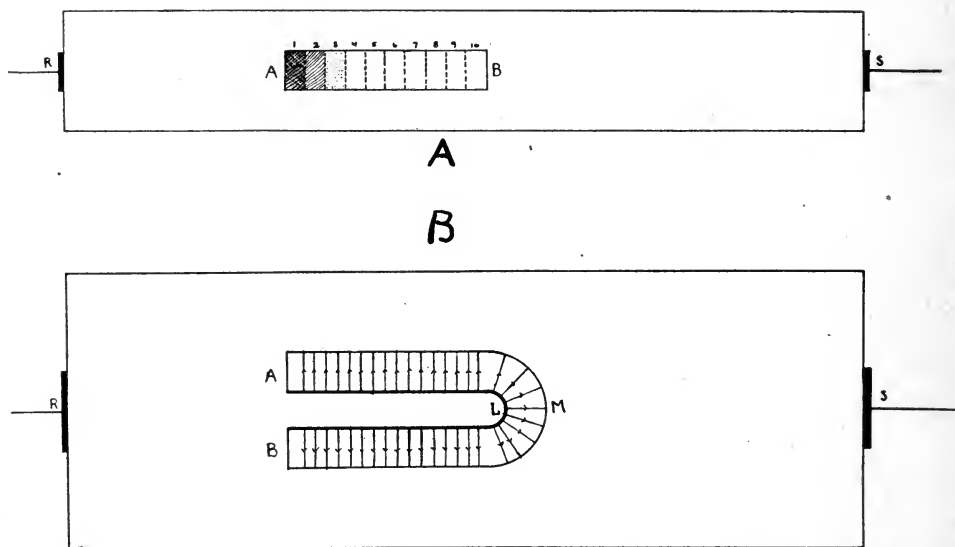
Fig. 2.—A, Diagrammatic representation of simple strip of muscle A-B immersed in conducting medium with electrodes attached at R and S. (see text). B, diagrammatic representation of horseshoe shaped piece of muscle immersed in conducting medium with electrodes attached at R and S. Muscle lined by Purkinje tissue (heavy line). Arrows represent course of excitation wave through muscle when point on internal surface is stimulated.

trogram obtained when the muscle contracts? From a consideration of the distribution of the iso-potential surfaces throughout a conductor when a difference of potential is generated within it, it appears that the asymmetric position of the muscle will not influence the direction of the deflections produced.[11] It may also be stated that it will not influence the amplitude of these deflections, providing that the distances R-A and B-S are relatively large in comparison with the distance A-B and the magnitude of the potential produced by the muscle.

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11. Private Letter, Einthoven to Lewis, 1918.

The truth of the last statement is shown by the following experiment. A series of electrocardiograms were taken from a normal subject in the manner illustrated by Figure 3. A line was drawn from the fourth costal cartilage (A) to a point on the left leg just below Poupart's ligament (E). This line was divided into four equal parts, 5 inches in length (A-B, B-C, C-D, D-E). By connecting in succession each two adjacent points to the terminals of the galvanometer four tracings were obtained (Fig. 4). It will be seen that the amplitude of the deflections falls off very rapidly in passing from lead A-B to lead
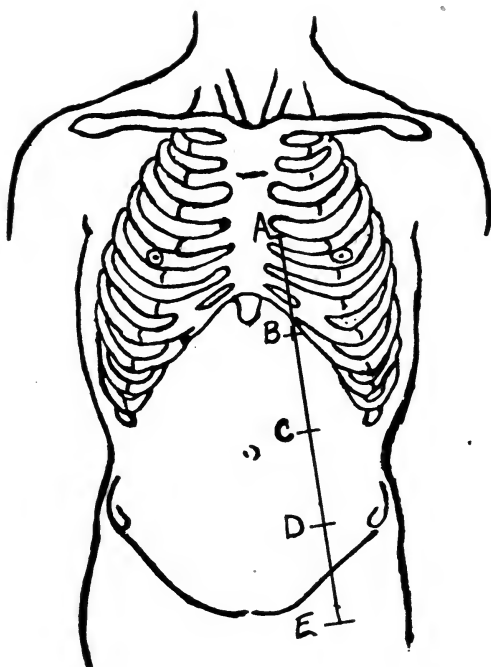
Fig. 3.—Diagram illustrating manner of taking electrocardiograms shown in Figure 4. A, fourth costal cartilage. Distances A-B, B-C, C-D and D-E equal and 5 inches in length.

C-D, and that no curve was obtained from lead D-E; that is, points D and E were of the same potential. The change in potential per unit distance decreases very rapidly, therefore, as the distance from the source of potential difference increases. We conclude that the asymmetric position of the muscle A-B with reference to the electrodes at R and S is of no importance so long as the distances R-A and B-S are relatively great.[12]

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12. In comparison with the distance A-B and the magnitude of the potential produced by the muscle.

It is not our purpose to discuss the form of the electrogram that might be expected to result from the activation of the muscle A-B. It is clear that if the muscle be stimulated at A so that the excitation wave travels from A to B, the first deflection that results will be directed upward. If the muscle is stimulated at B so that the excitation wave travels from B to A the initial deflection will be directed downward. But the exact form of the curve can only be determined by experiment; it depends on many factors, and among these the length of the muscle, the speed with which the excitation wave travels, and the form of the curve representing the development, duration and decline of relative negativity in a given section of the muscle. It is obvious that our present knowledge is insufficient to determine the

A-B   C-D

B-C

D-E
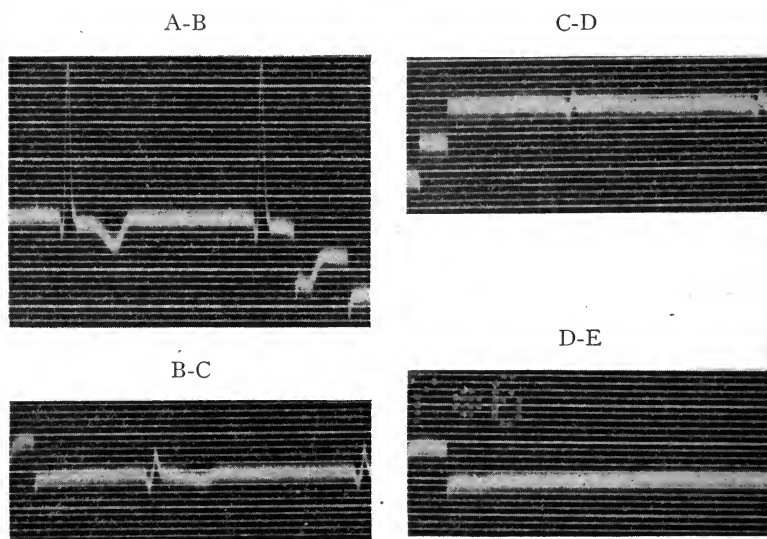
Fig. 4.—Electrocardiograms obtained by connecting successive points of Figure 3. Lead A-B by connecting points A and B to terminals of galvanometer, etc.

exact form of the electrogram produced by the activation of a given muscle, except by experiment. We can, however, predict the direction of the first deflection of this electrogram *providing we know the point of primary negativity and the course of the excitation wave through the muscle.*

Let us now direct our attention to a slightly more complicated muscle. Figure 2 B represents a simple strip of heart muscle bent into the shape of a horseshoe and immersed in a conducting medium with electrodes attached as before. If we stimulate this muscle at A or at B so that the excitation wave passes from A or B toward M, the first deflection will be upward. If we stimulate the muscle at M so that the excitation wave travels from M toward A and B the first

deflection will be downward. Can we conclude that an upward deflection indicates primary or preponderant activity at the base of the horseshoe (A or B), and that a downward deflection indicates similar activity at the apex of the horseshoe (M or L) if the point stimulated and the course of the excitation wave over the muscle is unknown? Suppose that the horseshoe is lined with Purkinje tissue which conducts the impulse at least ten times as rapidly as the remainder of the muscle. If any point on the inner surface of the horseshoe is stimulated, the course of the excitation wave over the horseshoe will then be nearly that represented by the arrows. The course of the excitation wave through the limbs of the horseshoe and the direction of the potential differences produced by the activation of these portions of the muscle will be roughly perpendicular to the line of lead and will have little or no effect on the electrogram. But the potential differences produced by the activation of the curved piece of muscle at the apex of the horseshoe will not be perpendicular to the line of lead; the internal surface (L) will show primary negativity with reference to the external surface (M). Since the slightly asymmetric position of the apical muscle with reference to the electrodes (R and S) will not affect the form of the electrogram produced, an upward deflection will result. If, however, the special conducting tissue lay on the external surface of the horseshoe instead of on the internal surface, the external surface (M) would show primary activity with reference to the internal surface (L) and a downward deflection would result. The effect of muscle activity at the apex of the horseshoe depends, therefore, on the course of the excitation wave over the muscle and not altogether on the position of the apex with reference to the remainder of the muscle.

To assume that preponderant muscle activity at the apex of the heart must cause a downward deflection in Lead II; or that corresponding activity at the base must cause an upward deflection in the same lead as has so frequently been done; to assume, as Fahr [4] has done, that when the electrical axis as determined by Einthoven's formula points to the left the preponderant muscle activity is on the right side of the heart, is totally unjustifiable. The facts, so far as they have been determined, indicate that the direction of the electrical axis at any instant corresponds in direction to what may be termed the average direction of the excitation wave at that instant. For example; the excitation wave passes from the endocardial to the epicardial surface of the free wall of the left ventricle; its average direction at this time is upward and to the left. The difference in potential produced by the activation of this region and the corresponding electrical axis is likewise directed upward and to the left; and the resulting deflection is upward in Lead I and downward in Lead III. When several areas

of muscle are passing into the excited state at the same time, the actual potential difference produced is the resultant of the potential differences produced in the various active areas and the electrical axis has the direction of this resultant. The direction of the potential difference produced by the activation of any portion of the ventricular muscle when the heart is activated in the normal way may roughly be determined by means of the scheme shown in Figure 1.

THE ELECTRICAL AXIS IN BUNDLE BRANCH BLOCK

Lewis [9] found on the analysis of the human dextrogram that the electrical axis was at first directed upward and to the left corresponding to the early spread of the excitation through the upper septum in this direction (Fig. 1); later it was directed downward and to the left as the lower portions of the septum became active. Then the electrical axis gradually rotated in a clockwise direction as the free wall of the right ventricle passed into the active state. These changes in the direction of the electrical axis are due to corresponding changes in the direction taken by the excitation wave (Fig. 1). An analysis of the human levogram showed a counter clockwise rotation of the electrical axis corresponding to successive involvement of the septum, apex and free wall (Fig. 1). Since the normal QRS group is a summation of levogram and dextrogram, it appears that Q 1 (Q of Lead I) is produced by the activation of the upper septum from the left side; that Q 3 is produced by the activation of the upper septum from the right side; that R 1 and R 3 are produced by the activation of the lower septum and adjacent portions of the apices of the two ventricles, and that S 1 is produced by the activation of the free wall of the right and S 3 by the activation of the free wall of the left ventricle.[9]

THE CRITERIA USED IN THE RECOGNITION OF BRANCH BUNDLE BLOCK

Let us now take up Carter's criteria for the recognition of bundle branch block in more detail. We shall speak mainly of right bundle branch block, as left branch block is a very rare condition in man.

The P-R Interval.—It is obvious that a lengthened P-R interval gives no direct evidence of bundle branch block. It indicates delayed conduction of the impulse through the A-V node or through the main stem of the His bundle. It is an aid in recognizing bundle branch block only because it indicates a lesion of the special conducting system, and because a lesion of one part of this system is apt to be accompanied by lesions of neighboring parts. No increase in the P-R interval occurs when bundle branch block is produced in animals by cutting the branches of the His bundle.

The QRS Interval.—It has been said that the increased duration of the QRS group in bundle branch block is mainly due to the slow spread of the excitation wave through the septum. The QRS interval will depend, therefore, on the thickness of the septum; it will probably be greater when there is great cardiac hypertrophy than when the heart is of more normal size. It is in patients with great cardiac hypertrophy that bundle branch block is most common, and in our experience the QRS interval of bundle branch block curves is usually much more than 0.1 second, and often more than 0.15 second. In experimental bundle branch block the QRS interval is about twice as great as the QRS interval of the physiologic electrocardiogram. In using the QRS interval as a criterion in recognizing bundle branch block, it must be remembered that as pointed out by Lewis[9] the QRS interval of left ventricular preponderance curves is often more than 0.1 second. This is due to the increased time taken by the excitation wave to traverse the thickened walls of the left ventricle. We believe that an increased QRS interval is the most reliable sign of bundle branch block; the greater the interval the greater its reliability.

Increased Amplitude of QRS.—The large amplitude of the QRS group in bundle branch block is mainly due to a lack of balance. Normally, the effects produced by the activation of the free wall of the left ventricle and those produced by the activation of the free wall of the right ventricle, which are oppositely directed (Fig. 1), come at the same time and tend to neutralize each other. In bundle branch block these two regions are not activated at the same time, so that the normal balance between them is disturbed and comparatively large deflections result. The actual amplitude of these deflections will depend on the amplitude of the levogram or dextrogram, whichever precedes, and the manner in which this is affected by the abnormal spread of the impulse in the ventricle whose activation is delayed. The amplitude of QRS is of less value than the QRS interval in recognizing bundle branch block. In dogs the amplitude of the initial deflection of right bundle branch block complexes is often less than the amplitude of the initial deflection of the physiologic electrocardiogram of the same animal.

The Exaggerated T.—The cause of the exaggerated T which is oppositely directed to the main deflection of the QRS group in bundle branch block curves is not well understood. It is believed that T represents the decline of the excited state in the ventricular muscle; just as the passage of a muscle from the inactive to the active state is accompanied by a change in its electrical state, so must the return of the muscle from activity to inactivity be accompanied by an electrical change of opposite sign. If each portion of the ventricular muscle

remained in the active state exactly the same length of time, and if deactivation took place as rapidly as activation, T should duplicate QRS in form, but should be oppositely directed. It seems probable that since T is several times as broad as QRS the deactivation process takes place very slowly in comparison with activation, and this may explain the difference in the form of the two deflections. The above ideas of the T deflection rest almost entirely on inference, for there is comparatively little experimental evidence bearing on the problem. We have recently carried out some experiments, however, which indicate that they are in the main correct.

Right branch block was produced in dogs by cutting the right branch of the His bundle. Various points on the surface of the right and left ventricles were then stimulated, sometimes at irregular, sometimes at regular intervals, by single induction shocks of the same strength. Each shock produced a slight notch in the electrocardiogram which could be used as a signal, and sufficient curves were taken to determine the effect of stimuli which fell in the different portions of the cardiac cycle. It was found that, in general, points on the surface of the left ventricle passed out of the refractory state from 0.02 to 0.03 second earlier than points on the surface of the right ventricle (Fig. 5). On the other hand, when left bundle branch block was produced the refractory period persisted longer over the surface of the left ventricle than over the surface of the right. These observations indicate that the ventricle that is first to be activated, first passes out of the active state. We believe that the large positive T of right bundle branch block (Lead II) in dogs is due to the early deactivation of the left ventricle in comparison with the right; and that the large negative T of left bundle branch block is due to early deactivation of the right ventricle in comparison with the left. This question will be discussed more fully in a later section of this article. The exaggerated T and the diphasic character of bundle branch block complexes are equal in importance to the increased QRS interval in their recognition.

Notching of QRS.—We cannot agree with Carter that notching of QRS is uncommon in normal electrocardiograms; we have observed it often and sometimes there is a very complicated multiple notching in Lead III. There is, however, a considerable difference between the notching of normal electrocardiograms and the notching of bundle branch block complexes. In the former, the notching is practically confined to the lead of smallest amplitude (usually Lead III) or at least it occurs relatively close to the base line. In the latter the notch is usually present near the apex of QRS in leads of large amplitude; it may be but often is not most marked in the lead of least amplitude. Although there may not be any essential difference between these two
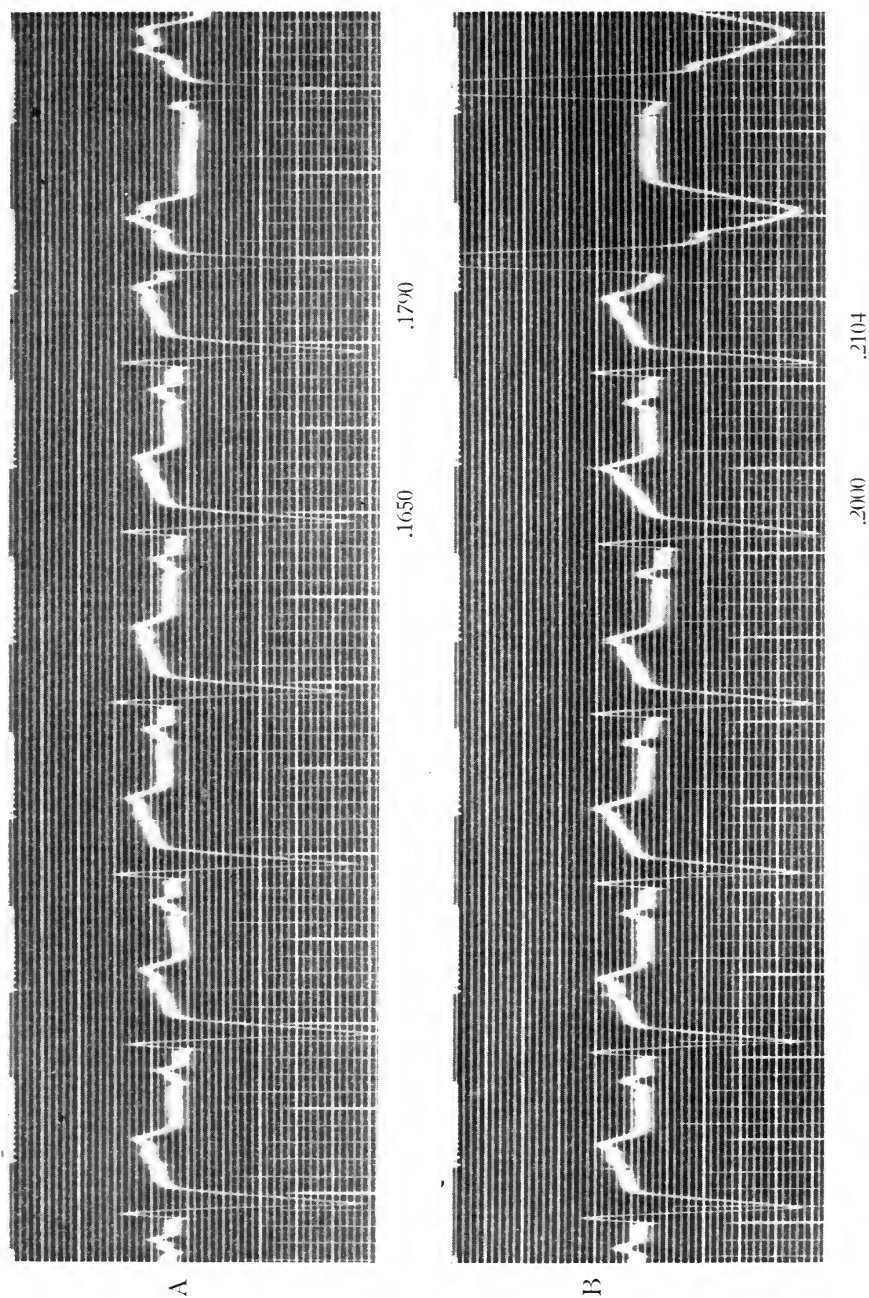
Fig. 5.—Right bundle branch block produced in dog by cutting right branch of His bundle (Lead II). A, effect of rhythmic stimulation of left apex by break induction shocks. Signal above and also on electrocardiograms. Refractory phase ends between .1650 and .1790 second after Q. B, effect of stimulating right conus region in same way. Refractory phase ends between .2000 and .2104 second after Q.

types of notching, except that of degree, yet we believe that they differ entirely in their practical significance. In order to bring out the reasons for this belief it is necessary to discuss the manner in which notches are produced.

According to Einthoven's [13] scheme of the equilateral triangle for representing the relationship between the three leads (Fig. 6), the height of a deflection in a given lead at a given instant is dependent on two factors; the manifest potential difference (E) which is a definite fraction of the absolute potential difference developed by the heart at that instant, and the cosine of the angle between the direction
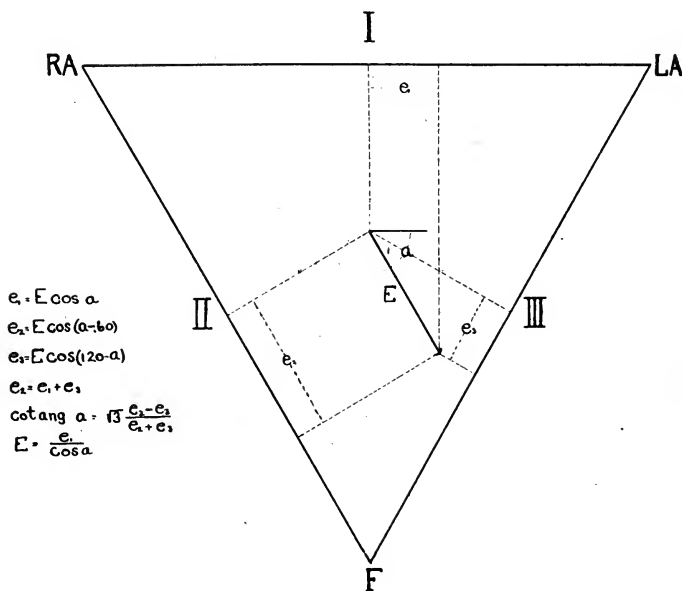
Fig. 6.—The equilateral triangle of Einthoven. I, Lead I; II, Lead II; III, Lead III. R A, right arm; L A, left arm; F, left or right foot. E, manifest potential difference produced by heart at any instant. e1, resulting deflection in Lead I; e2, resulting deflection in Lead II; e3, resulting deflection in Lead III. *a*, angle made by E with I; *a-60*, angle made by E with II; 120-*a*, angle made by E with III.

in which this potential is developed and the line of lead. It may be shown that if the angle made with the line of Lead I is *a,* then the angle made with the line of Lead II is *a-60* and the angle made with the line of Lead III is 120-*a* (Fig. 6).

13. Einthoven, Fahr, and de Waart: Ueber die Richtung und die manifeste Grösse der Potentialschwankungen in menschlichen Herzen und über den Einflusz der Herzlage auf die Form des Elektrokardiograms, Arch. f. d. ges Physiol. **150**:275, 1913.

During the QRS interval both the scalar magnitude of E and its direction (i. e., angle a) are constantly changing. In Figure 7 (the necessary data for the construction of this figure were taken from the
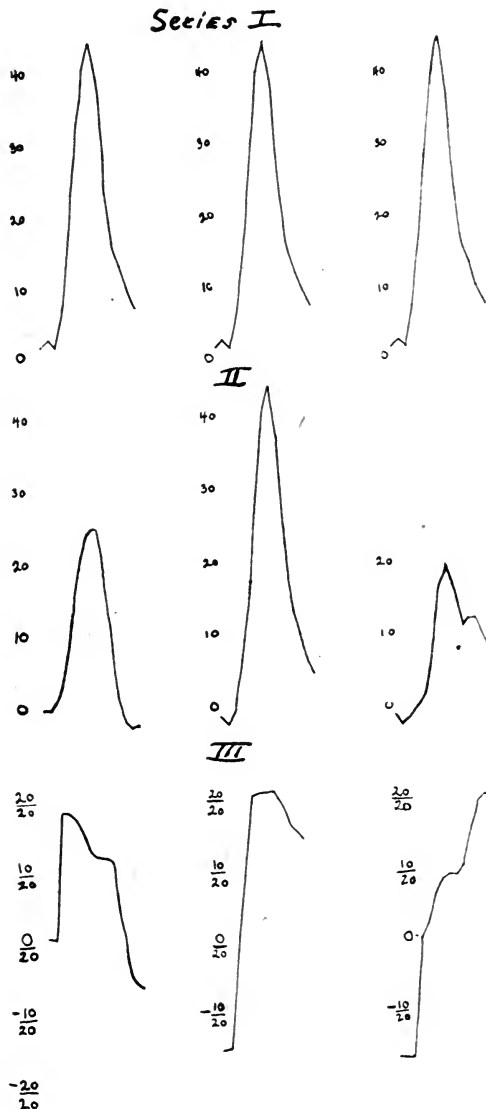
Fig. 7.—(Data taken from paper by Lewis[9].) Series I, three identical curves representing the changes in E (Fig. 6) during QRS interval. Series II, QRS group in Leads I, II and III. Series III, three curves representing changes in cosine a, cosine $(a\text{-}60)$, and cosine $(120\text{-}a)$ during QRS interval.

work of Lewis[9]) the rapid increase and subsequent decline in the value of E during the QRS interval are shown by the first series of

curves (the three curves are identical). The first curve of the lowest series shows the corresponding variations in the value of cosine a, and the last two curves of this series show the variations in the values of cosine $(a\text{-}60)$ and cosine $(120\text{-}a)$, respectively. The middle series of curves represents the QRS groups of the three leads in order; the ordinates of these curves are equal to the products of the ordinates of the first series and the corresponding ordinates of the last series.

It is obvious that the changes in a, $a\text{-}60$ and $120\text{-}a$ produced by changes in the direction of the vector E, if measured in degrees, will be the same. The corresponding changes in the cosines of these angles, however, will differ greatly, for the change in cosine per degree is much more rapid near 90 degrees than near zero degrees. Since, moreover, the deflection in a given lead is smallest when the electrical axis is perpendicular to the line of lead (the deflection in Lead I, for example, is smallest when a is 90 degrees) and largest when the electrical axis is parallel to the line of lead, it follows that the QRS group of largest amplitude will most faithfully reproduce the variations in the scalar magnitude of E that take place during the QRS interval; and the QRS of least amplitude will most faithfully record the changes in the direction of the vector E which occur during this interval. Thus QRS of Lead II in Figure 7 closely resembles the curve of series I, while QRS of Lead III resembles it least and shows a distinct notch produced by the irregular movements of the electrical axis.

It will be seen that notching will tend to be produced by irregularities in the movements of the electrical axis under the following conditions: (1) When there is a rapid irregular rotation of the electrical axis toward the perpendicular to the line of lead while the scalar magnitude of E is increasing; (2) when there is a rapid irregular rotation of the electrical axis away from the perpendicular to the line of lead while the scalar magnitude of E is decreasing; (3) when there is a change in the direction of the rotation of the electrical axis from clockwise to counterclockwise or vice versa. Notching in a given lead will occur only when the irregularity in the movement of the electrical axis takes place while the electrical axis is relatively close to the perpendicular to the line of that lead; it will usually be most conspicuous, therefore, in the QRS of least amplitude (Fig. 7): When the heart is activated in the normal fashion, left ventricular effects which tend to cause a counterclockwise rotation of the electrical axis and right ventricular effects which tend to cause a clockwise rotation of the electrical axis occur simultaneously. As the effects of now one and now the other ventricle preponderate, the electrical axis shifts first this way and then that. These frequent and rapid changes in the

position of the electrical axis are mainly responsible for notching of the normal QRS group.

Theoretically, notches may be produced by irregularities in the growth and decline of the manifest potential difference; that is, the curve which represents the variations in the scalar magnitude of E may be notched. Such notches will be reproduced most faithfully in the QRS of greatest amplitude; they may, of course, either be accentuated or diminished by simultaneous irregularities in the movements of the electrical axis which are apt to accompany them. It is probable that the notches which occur on the QRS group of bundle branch block curves are of this type. The curves of right bundle branch block in dogs almost invariably show a distinct notch on the posterior limb of QRS 2 (QRS of Lead II), and it seems probable that this notch is due to a sudden change in the scalar magnitude of E, accompanied perhaps by a sudden change in the direction of the electrical axis, resulting from the sudden spread of the excitation wave in the right ventricle after it has pierced the septum. In fact, we are inclined to believe that this notch is due to the superimposition of Q' of the dextrogram on the ascending limb of the levogram. A similar but more prominent notch which often occurs near the apex of QRS in left bundle branch block in dogs may be due to the superimposition of R' of the levogram on the descending limb of the dextrogram.

That the sudden involvement by the excitatory process of a new area of muscle may produce notching is shown by Figure 8. It will be noted that not all the extrasystolic complexes of this figure are of the same form; some of them show a distinct notch on the posterior limb of QRS. All of the extrasystoles shown occurred late in diastole, but it is those which occur latest which show the notch. The position of this notch with reference to the previous P indicates that it occurs after the normal P-R interval, and it is undoubtedly due to the sudden involvement of an area of muscle that is activated by the supraventricular stimulus before the extrasystolic stimulus has reached it.

This curve is an interesting one from another standpoint. It indicates that all of the ventricular muscle has not passed into the refractory state until QRS is complete. The notched extrasystolic complexes show that the muscle which normally first receives the supraventricular stimulus is still irritable when the extrasystolic QRS is almost complete, and the shortened initial deflections and modified final deflections of cycles A 5 and B 1 indicate that the extrasystolic stimulus still finds the surrounding muscle irritable when the normal stimulus has activated a large portion of the ventricular muscle. When the normal stimulus reaches the ventricles after the extrasystolic QRS is complete, however, it finds the ventricles refractory.
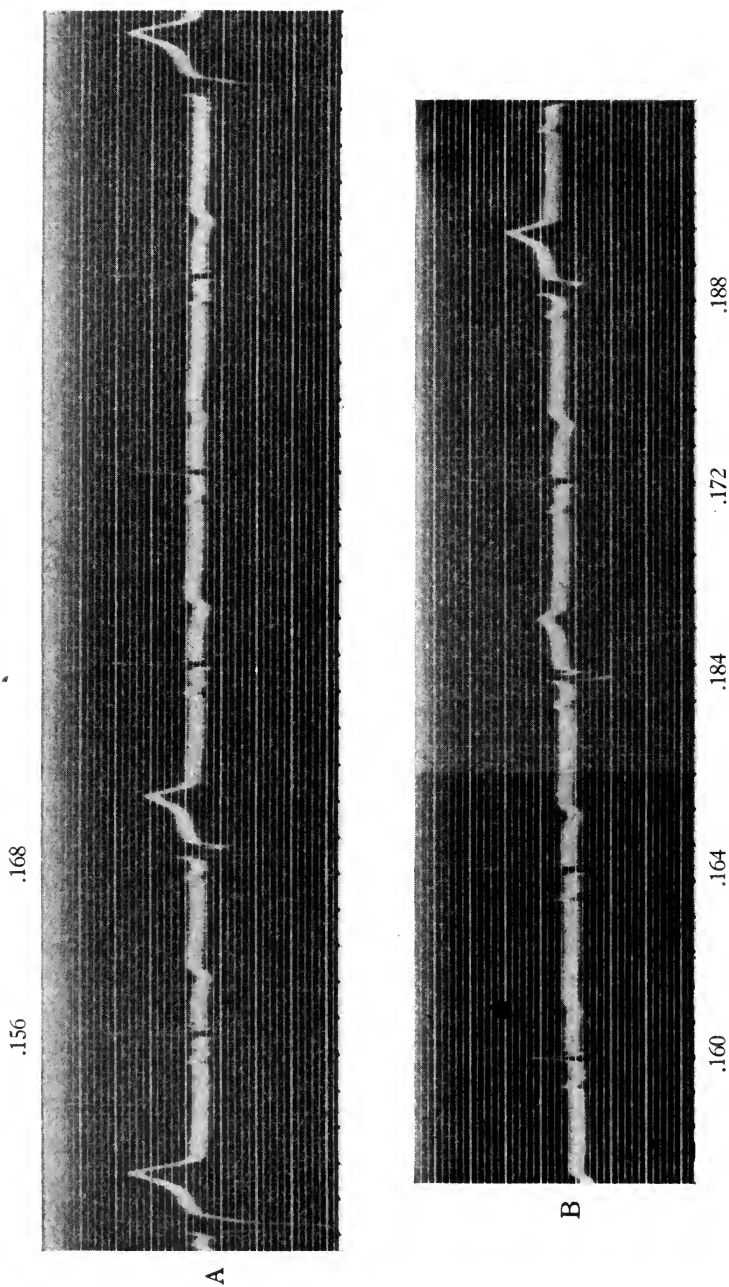
Fig. 8.—Electrocardiogram from apparently normal individual (Lead III). Extrasystoles occurring late in diastole and showing interference between normal and extrasystolic stimuli. Every second complex represents a response partly to the normal and partly to the extrasystolic stimulus.

In concluding the subject of notching, it may be said that it is not an essential feature of bundle branch block complexes; it is frequently absent in man; but when it occurs it is suggestive, especially if it falls near the apex of QRS in a lead of large amplitude.

DIFFICULTIES ENCOUNTERED IN THE DIAGNOSIS OF BUNDLE BRANCH BLOCK

Typical examples of right bundle branch block are recognized without difficulty (Fig. 9). The diphasic character of the ventricular
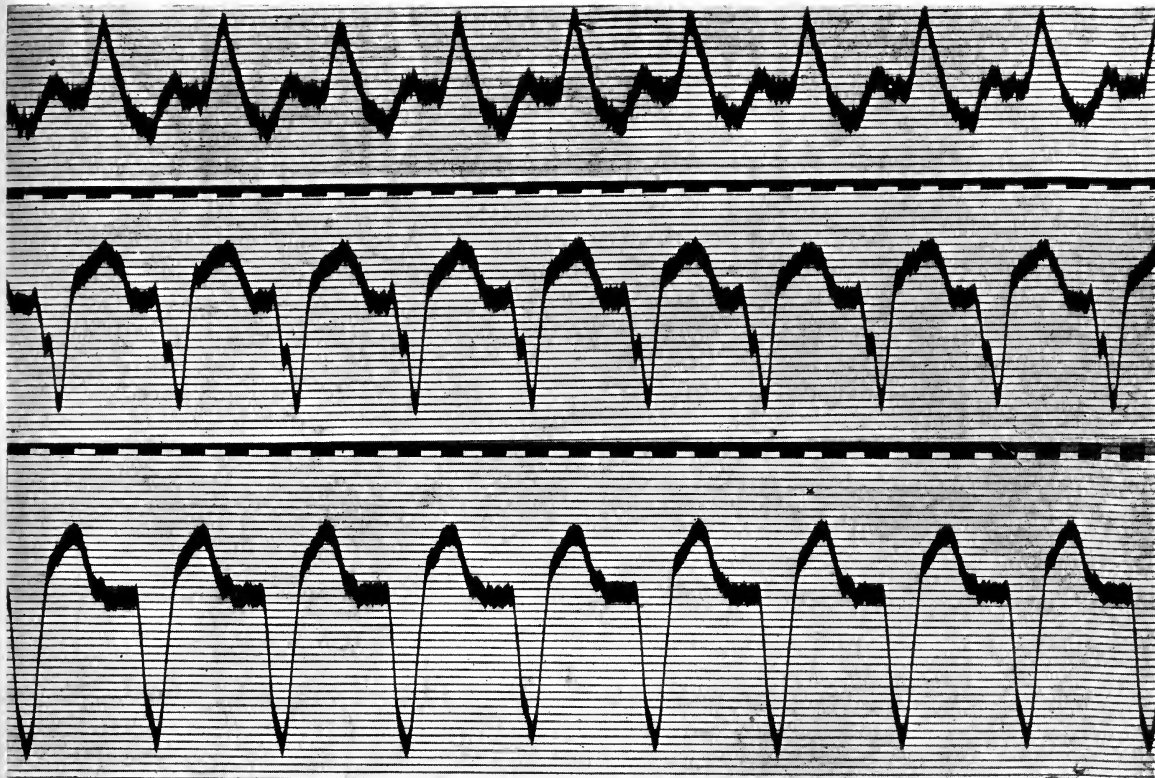
Fig. 9.—Right bundle branch block. QRS equals 0.179 second.

complex, its relatively large amplitude, the notch which so frequently occurs near the apex of QRS, the long QRS interval often measuring more than 0.15 second, are sufficiently distinctive. Comparatively few of the aberrant electrocardiograms observed clinically, however, are typical examples of this condition. Especially confusing are the transitions which are seen between the type of ventricular complex characteristic of left ventricular preponderance (Fig. 10) and the type

characteristic of right bundle branch block (Figs. 9 and 14). Such transitional complexes are shown in Figures 11, 12 and 13. According to Lewis,[9] the direction of the terminal deflection T serves to distinguish between curves of these two types; bundle branch block complexes are typically diphasic, preponderance complexes are not, but show the same variations of T that occur in the normal ventricular complex. One who attempts to interpret large numbers of clinical curves soon finds, however, that at least one-half of the left ventricular
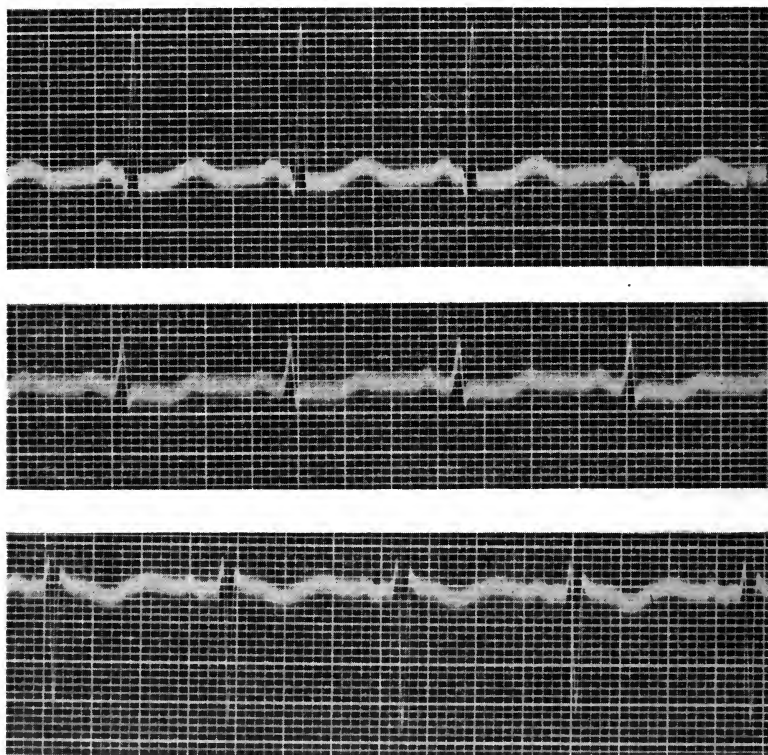
Fig. 10.—Left ventricular preponderance. P-R 0.12, QRS 0.073. T1 positive and T3 negative.

preponderance curves that he encounters show the same type of T as do curves of right bundle branch block; T 1 is negative and T 3 positive, so that the ventricular complex is diphasic in Leads I and III. QRS of Lead II is less frequently negative in preponderance curves than in right bundle branch block, but this difference is not sufficiently distinctive to be of use in differentiating the two types. The QRS interval of preponderance curves is often increased and the transitional curves spoken of show QRS intervals varying from normal to

0.15 second. No sharp line can be drawn, therefore, between the curves of left ventricular preponderance and those of right bundle branch block, and the interpretation of many aberrant electrocardiograms consequently remains doubtful.

The cause of the frequent occurrence of a downwardly directed T 1 and a large upwardly directed T 3 in left ventricular preponderance curves is not known. Perhaps this type of T is a less sensitive indicator of left ventricular preponderance than the well-known deformity of
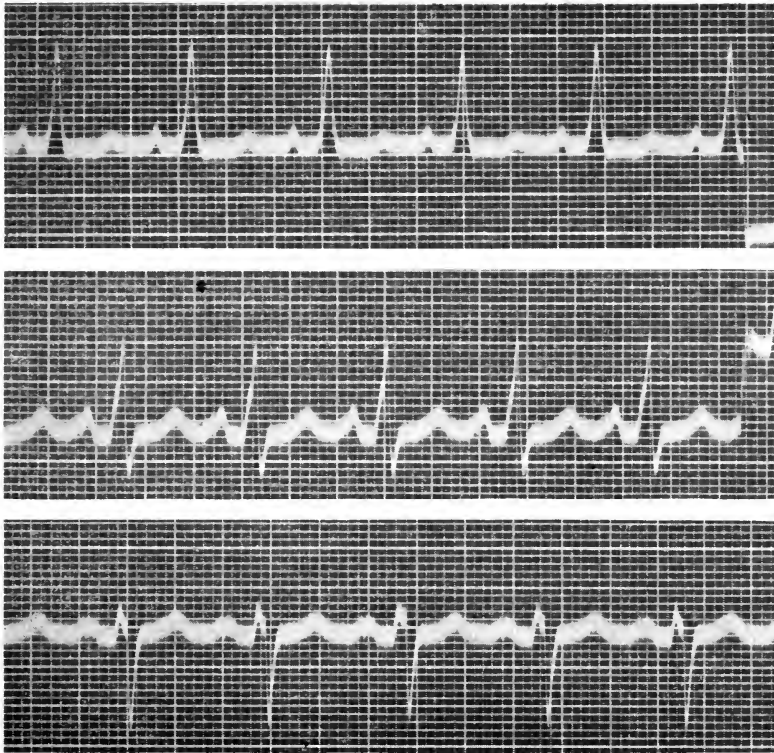
Fig. 11.—Left ventricular preponderance or perhaps slightly defective conduction through right branch of His bundle. P-R, 0.16; QRS, 0.108.

the QRS group which is used as the main criterion of this condition. Nevertheless, many patients with undoubted left ventricular preponderance show T waves of normal type. Inversion of T in Lead I has long been considered a sign of myocardial changes, and Eppinger and Rothberger [2] suggest that it may indicate slightly defective conduction through the right branch of the His bundle. There is some evidence in favor of this view, but far less than enough to make it acceptable. In one instance we have obtained curves of left ventricular preponder-

ance and subsequent curves of right bundle branch from the same individual. T 1 of the preponderance curves was negative, and this might be considered the first sign of the bundle branch block which appeared a few days later; but T 2 was negative in the first and positive in the second set of records, so that this explanation is very doubtful in this instance. Many of the preponderance curves showing the
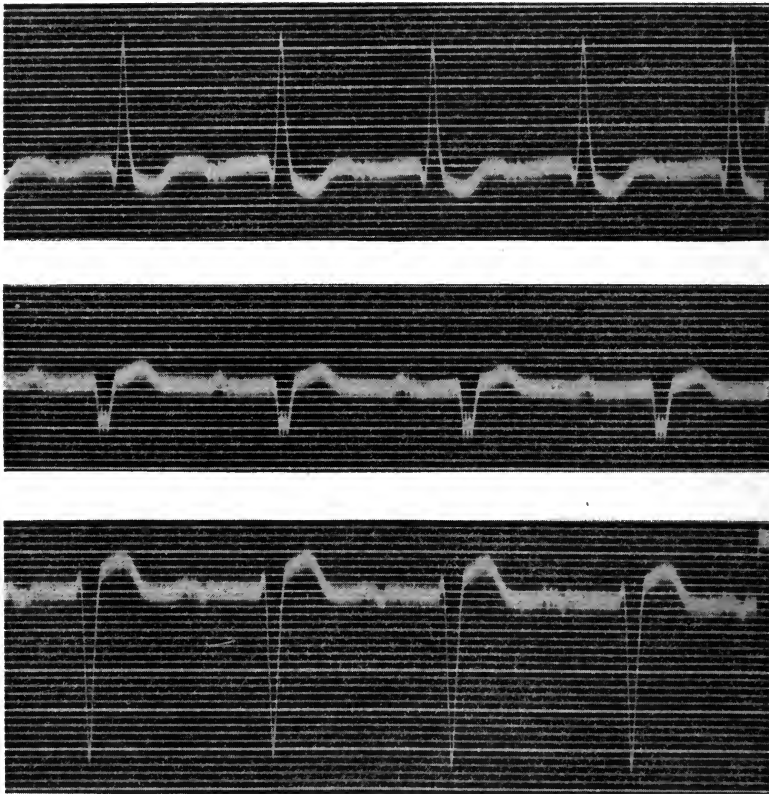
Fig. 12.—Transitional in form between left ventricular preponderance and right bundle branch block. Probably delayed conduction through right branch. P-R, 226; QRS, 0.096.

type of T under discussion have a relatively normal QRS interval which practically rules out disturbances of intraventricular conduction; in others the QRS interval is definitely increased, and when this is the case the explanation offered by Eppinger and Rothberger deserves consideration.

THE EFFECT OF DELAYED CONDUCTION THROUGH THE BRANCHES OF THE HIS BUNDLE ON THE ELECTROCARDIOGRAM

The question of the effect of lesions of the branches of the His bundle of such a character as to delay without completely interrupting the passage of the impulse through them has received less consideration than it merits. When a clamp is placed on the main stem of the His
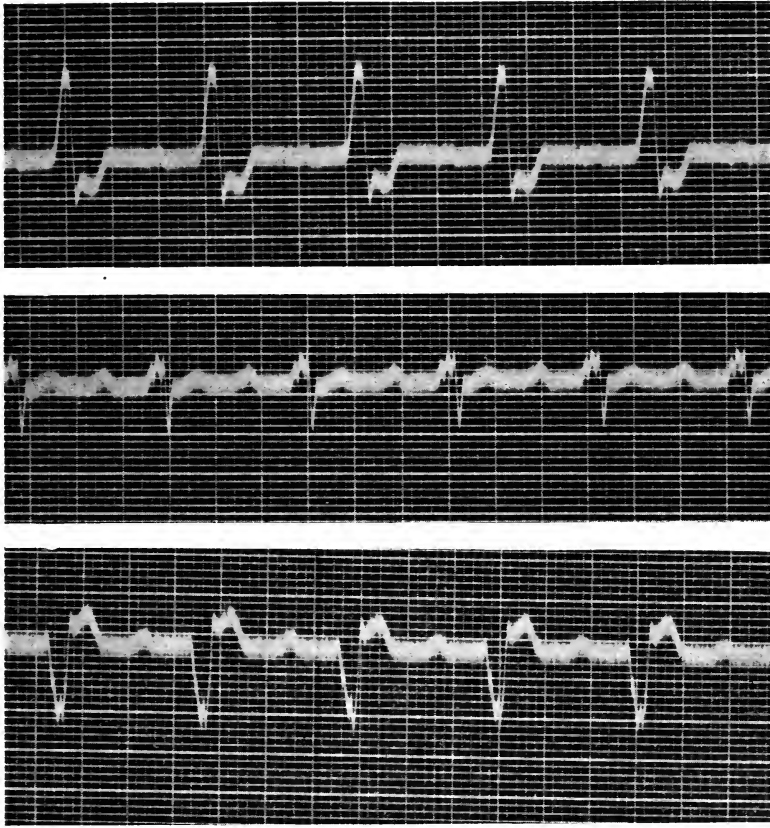
Fig. 13.—Similar to Figure 12, but of smaller amplitude. P-R, 0.24; QRS, 0.114.

bundle and tightened, complete A-V block is produced. If the clamp is then loosened, recovery may take place suddenly or all the stages of partial A-V block may be obtained from frequently blocked auricular beats to simple prolongation of the As-Vs interval. By analogy we might expect similar results from clamping and then releasing the chief branches of the His bundle which have the same structure as the main stem. But the relations are somewhat different. If we produce bundle branch block in this way, the impulse is not prevented, as in

complete A-V block, from reaching the farther side of the blocked area. It does so by passing down the unclamped branch and thence through the ventricular septum to the Purkinje network of the ventricle normally supplied by the clamped branch.

Perhaps for this reason, perhaps for some unknown reason, nothing comparable to the dropping out of ventricular beats in partial A-V block ordinarily occurs as a result of lesions of the branches of the His bundle, so long as the heart is beating regularly. When the heart
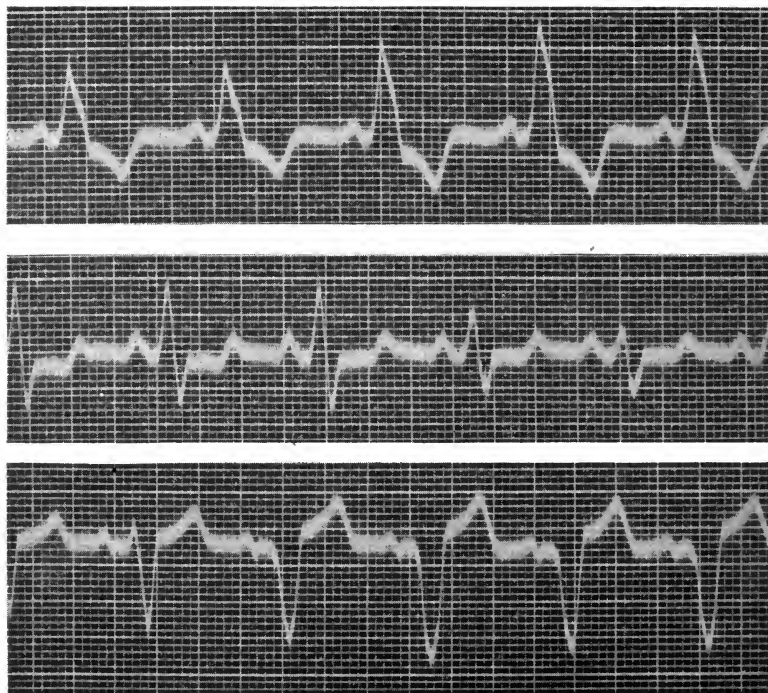
Fig. 14.—Complete right bundle branch block. Variations in form of complexes due to forced respiration with changes in position of heart. P-R, 0.14; QRS, 0.142.

is beating irregularly, however, as in auricular fibrillation, variations in the length of the diastolic rest period and consequently in the functional recovery of parts through which the passage of the impulse is delayed but not completely interrupted must occur. When a path is completely destroyed, variations in its rest period cannot affect its conductivity. We may say therefore, that we have complete bundle branch block or delayed conduction through one of the branches of the His bundle,

but we rarely have partial bundle branch block if "partial" be used in the same sense as in A-V block. It may also be stated that the ventricular complexes which indicate delayed conduction through the branches of the His bundle will tend to show variations in form with variations in the length of diastole.

The subject of delayed conduction through the branches of the His bundle has not previously been studied experimentally, and we wish to report briefly here some experiments relating to this subject, reserving the details for a future communication. We produce right bundle branch block in dogs by cutting the right branch of the His bundle. The right ventricle is then stimulated by single induction shocks. When the stimulus falls during the refractory period of the point stimulated no response occurs. When the stimulus falls between T and the following P, a typical right ventricular extrasystole is obtained. When the stimulus falls during the latter part of the P-R interval or on the first part of QRS, the complexes obtained are transitional in form between the extrasystolic complexes and the right bundle branch block complexes. This result might be expected. In right bundle branch block the left ventricle receives the impulse at the normal time, but the activation of the right ventricle is delayed. There is a short period, therefore, during which the left ventricle is passing into the active state while the right ventricle is still quiescent and not yet refractory to stimulation. Stimulation of the right ventricle during this period produces a response, and the resulting ventricular complex is a combination of the normal levogram and the extrasystolic dextrogram. The extrasystolic dextrogram is not usually of exactly the same form as the normal dextrogram obtained by producing left branch bundle block, but it resembles the latter closely in many instances. When the stimulus falls at the proper instant, normal levogram and extrasystolic dextrogram begin simultaneously, and a complex of the normal type results. When the dextrogram precedes the levogram, the same effect is produced as would be produced by delayed conduction through the left branch of the His bundle. When the levogram precedes the dextrogram the same effect is produced as would be produced by delayed conduction through the right branch of the His bundle. We may, therefore, obtain all the transitions between right bundle branch block complexes and the complexes of right ventricular extrasystoles which closely resemble the complexes of left bundle branch block.

We may illustrate our method by some curves from a sample experiment. In this instance an attempt to cut the left branch of the His bundle produced complexes characteristic of left bundle branch block (Fig. 15 B) which persisted for a short period and then gave
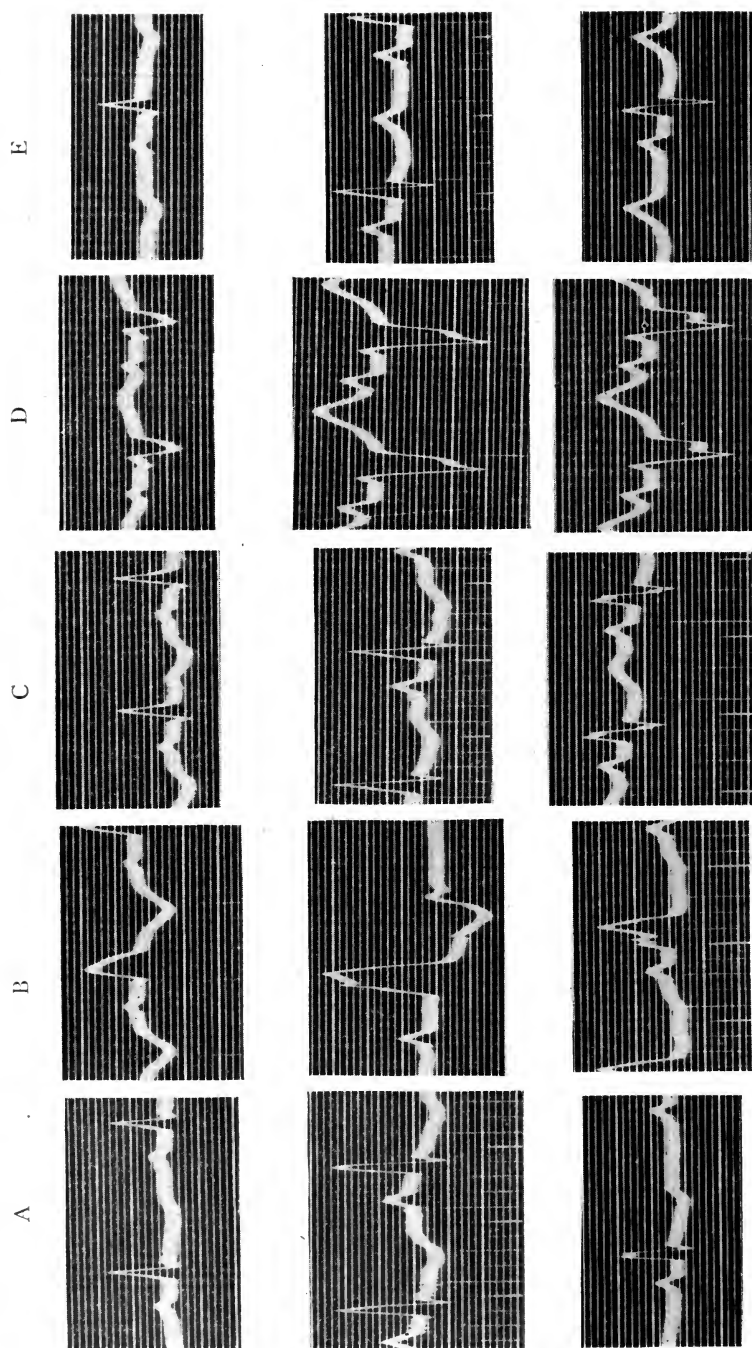
Fig. 15.—A, control curves from dog; B, left bundle branch block; C, recovery; D, right bundle branch block; E, recovery.

place to complexes (15 C) almost exactly like those of the control curves (15 A). Right bundle branch block was then produced by pressure on the right branch of the His bundle; the characteristic complexes (15 D) of this lesion appeared and persisted for about one
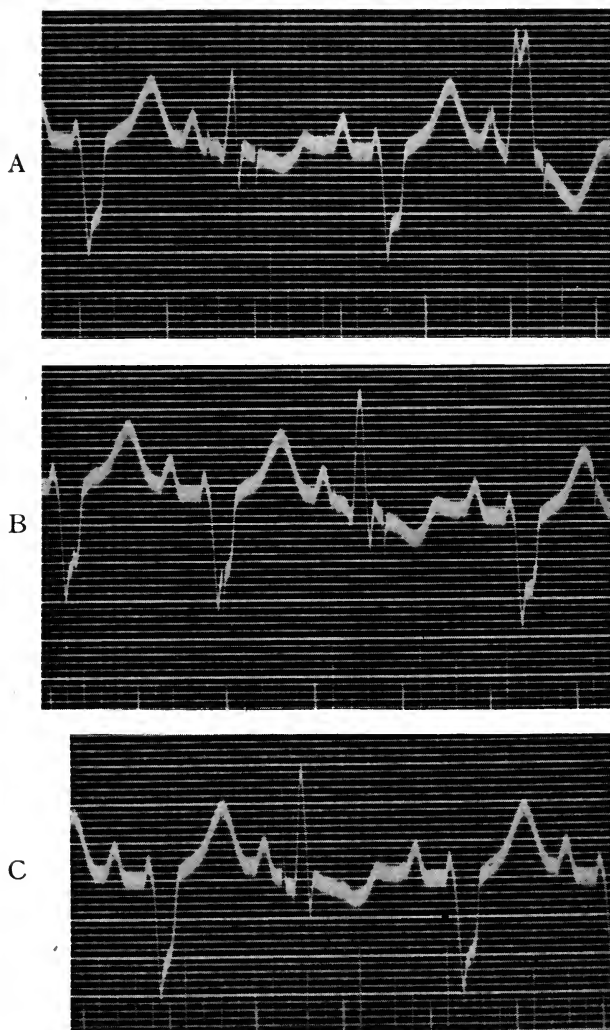

Fig. 16.—Dog 7. Lead II. Right bundle branch block. Reproduction of normal complex by stimuli which fall during P-R interval.

and one-half hours finally giving place to complexes of normal type (15 E). During the time that right bundle branch block was present the right ventricle was stimulated at irregular intervals by single induction shocks. The extrasystolic dextrogram produced (Fig. 16 A)

closely resembled the normal dextrogram obtained earlier in the experiment when left bundle branch block was present. When the stimulus fell at exactly the proper instant the normal ventricular complex was reproduced (Fig. 16 A, B, C). Many complexes transitional in form between the complexes of normal type and those characteristic of right and left bundle branch block were also obtained (Fig. 17). These transitional complexes show the following characteristics: (1) a QRS interval intermediate between that of the normal complexes and that of the bundle branch block complexes, and (2) a T deflection transitional in type between that of the normal complexes and that of the bundle branch block complexes. All the transitional complexes except those which most closely approach the normal complex in form are diphasic and the general resemblance of these complexes to those so-called preponderance curves which are diphasic in Leads I and III, and which show an increased QRS interval, is striking. We are inclined to believe that many of the curves of this type obtained from patients are due to delayed conduction through the right branch of the His bundle.

The transitional complexes obtained by experiments such as the one described above are of value in analyzing the T deflection. We have previously given evidence indicating that the upstroke of T (Lead II) of right bundle branch block curves from the dog is mainly a left ventricular effect due to the early deactivation of the left ventricle in comparison with the right. If it is true, as indicated by our previously mentioned experiments on the duration of the refractory state at various points on the surface of the ventricles in bundle branch block, that the ventricle first activated first becomes inactive, and if it is true that T is due to the deactivation of the ventricular muscle; the upstroke being mainly a left and the downstroke mainly a right ventricular effect (Lead II in dogs); then the direction of T of the transitional complexes under discussion should be mainly dependent on whether the right or the left ventricle is first activated. That this is the case can be verified by an inspection of Figure 17. It will be noted that when the levogram precedes the dextrogram by an appreciable interval, T is positive, and when the dextrogram precedes the levogram by an appreciable interval, A is negative. When left and right ventricular effects are nearly simultaneous the direction of T seems to depend on which of the two ventricles produces effects of greatest amplitude. Furthermore, since the left ventricle is activated by the stimulus which descends from the auricles, the levogram follows the P wave by an interval equal to the P-R interval. The upstroke of T, if it is a left ventricular effect, should also follow P by a definite interval. This is approximately true for all transitional complexes, except those which approach the normal type of complex closely; in
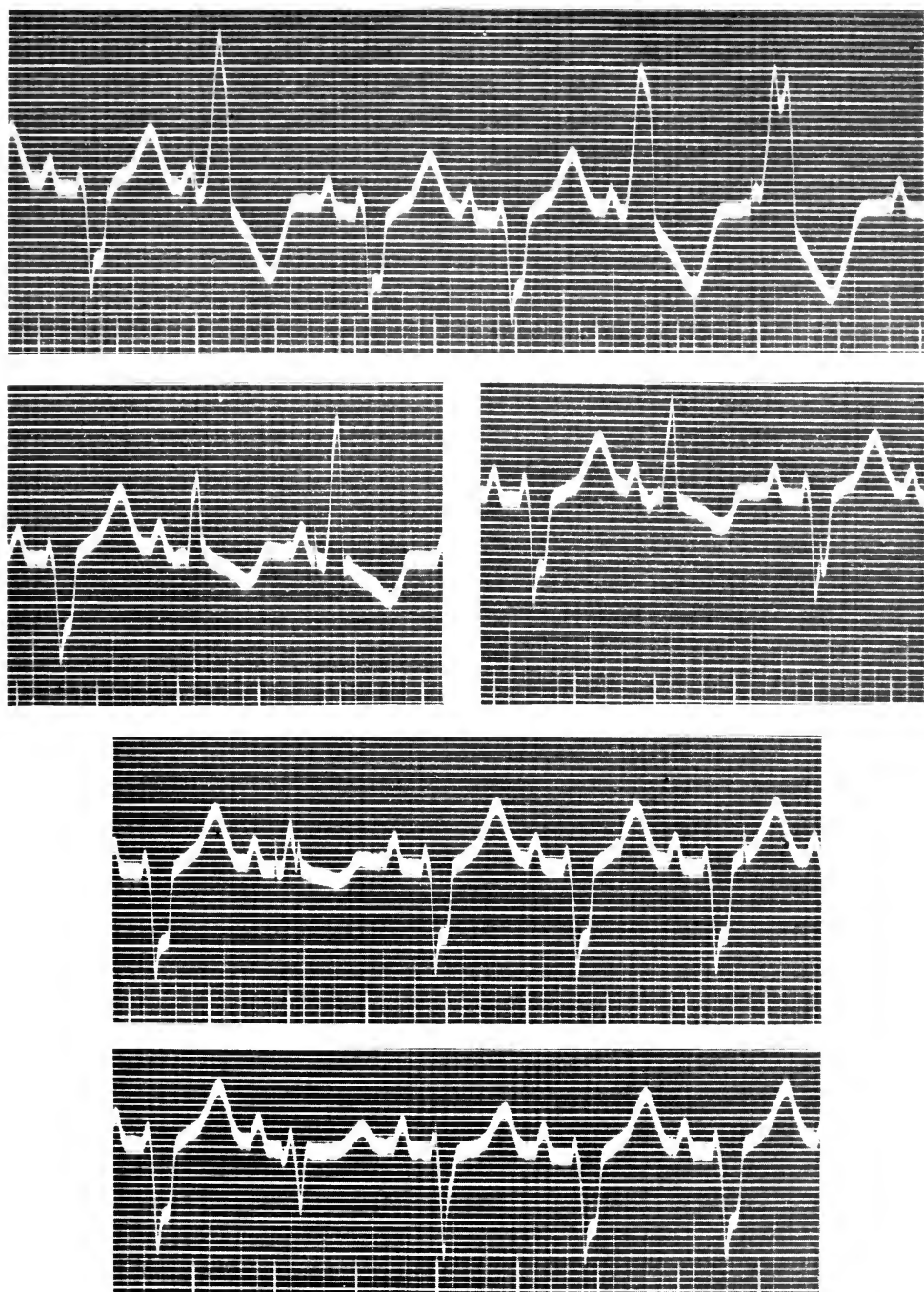
Fig. 17.—Dog 7. Lead II. Right bundle branch block. Production of complexes transitional in form between right bundle branch block complexes and complexes of right ventricular extrasystoles.

these the levogram and dextrogram begin almost at the same time and
the corresponding upstroke and downstroke of T are also nearly simul-
taneous. In such cases the beginning of the upstroke cannot be iden-
tified. All the evidence so far obtained indicates, therefore, that the
interpretation of T previously given is, in the main, correct.

CLINICAL OBSERVATIONS ON DELAYED CONDUCTION THROUGH THE
BRANCHES OF THE HIS BUNDLE

In addition to the experimental evidence given above, we have
made certain clinical observations which suggest that diphasic ven-
tricular complexes are often due to delayed conduction through the
branches of the His bundle. Figure 18 shows an electrocardiogram
from a patient, aged 59, who showed on physical examination cardiac
enlargement and arteriosclerosis and who was believed to be suffering
from myocarditis. There is a tall R 1 and a deep S 3; T 1 is small and
T 3 strongly positive. Lead II resembles Lead III, but is of smaller
amplitude. The QRS interval is about 0.1 second. Numerous extra-
systoles, auricular and ventricular, are shown. In Figure 19 another
curve (Lead III) from the same individual is shown. In this figure
there is an interpolated ventricular extrasystole (cycle A_2) of which
the QRS interval (0.074) is considerably less than that of the sequen-
tial beats (0.1). There is also an auricular extrasystole (cycle A_4)
of which the QRS interval (0.116) is considerably greater than that
of the sequential beats. In analyzing this electrocardiogram we have
used a general principle which may be stated as follows: No single
stimulus, in whatever part of the heart it originates, can activate all of
the ventricular muscle in a sufficiently short time to give a ventricular
complex the QRS interval of which is less than that of the sequential
beats unless there is defective conduction through one of the main
branches of the His bundle. This statement is based on the following
considerations: The QRS interval is a measure of the time taken by
the impulse to complete its course over the ventricular muscle. This
time will be shortest when the stimulus passes into the conducting
systems of both ventricles simultaneously. A stimulus can only reach
the conducting systems of both ventricles simultaneously when it arises
above the bifurcation of the His bundle or when it arises in the cen-
tral region of the interventricular septum. Under normal conditions
a stimulus which arises in the central part of the septum can hardly
pass over the ventricular muscle more quickly than the normal supra-
ventricular stimulus. When there is defective conduction through one
of the chief branches of the His bundle, the entrance of the normal
stimulus to the corresponding ventricle is delayed so that it can not
reach the endocardial surface of both ventricles simultaneously.
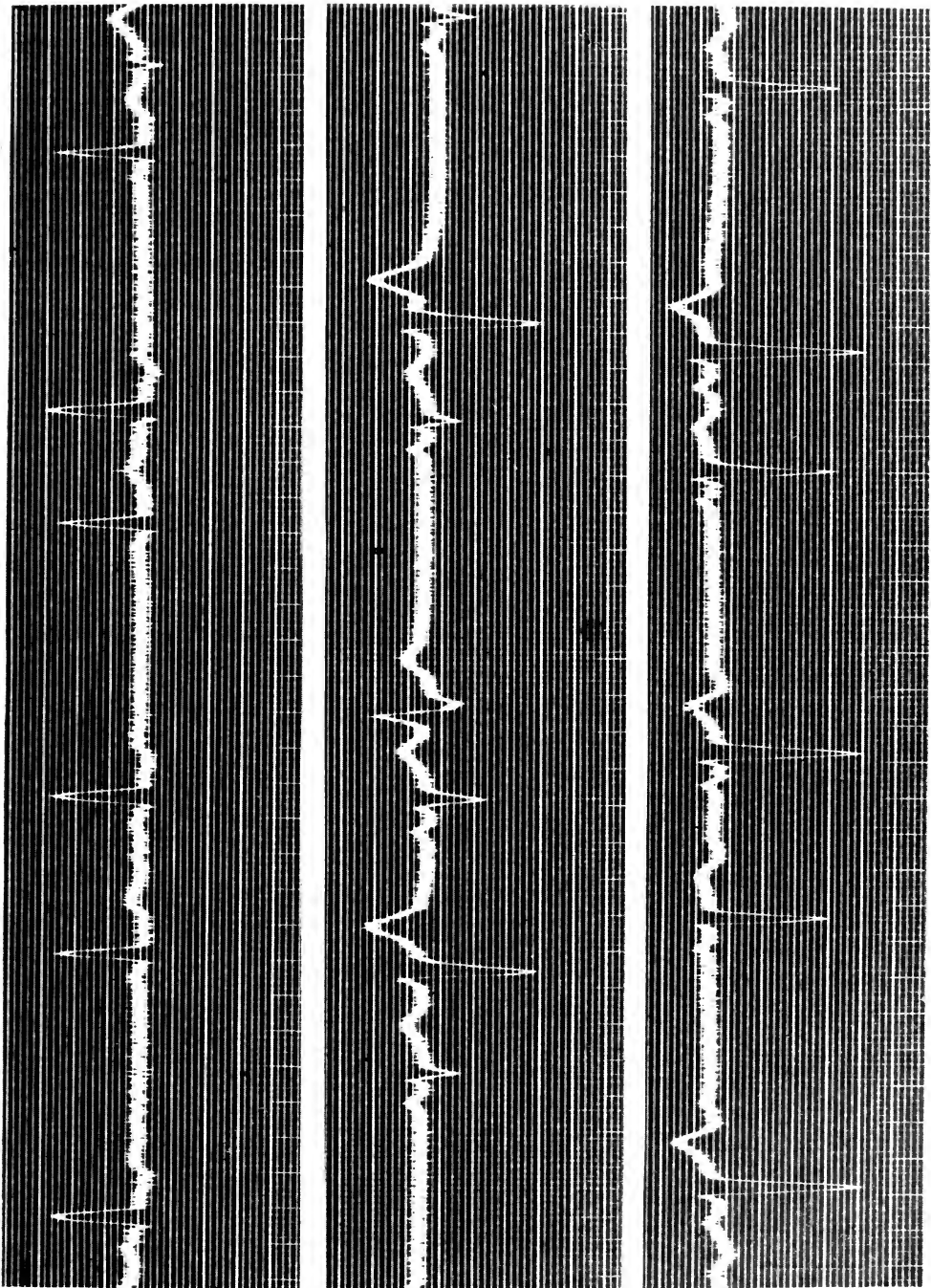
Fig. 18. E. K. G. 3658. Probably defective conduction through right branch of His bundle. Ventricular extrasystoles. Auricular extrasystoles.

stimulus arising in the septum, however, may still do so, for it may reach the Purkinje system of the affected ventricle below the blocked area.

Assuming that the ventricular extrasystole (cycle A_2, Fig. 19) was due to a single stimulus and not to two stimuli, one arising in each ventricle, which occurred simultaneously, then delayed conduction through the right branch of the His bundle was probably present in the heart from which this curve was obtained. We interpret Figure 19 in the following way. There was defective conduction through the right branch of the His bundle. The stimuli which came down from the auricles had to pass the blocked area to reach the right ventricle; hence the abnormal form of the ventricular complex and its increased QRS interval. The stimulus which gave rise to the auricular extrasystole (cycle A_4) also had to pass the blocked area which had had less time to recover than in the case of the sequential beats; the resulting ventricular complex is more abnormal than that of the sequential beats. The ventricular axtrasystole (A_2) was of septal origin and reached both ventricles at about the same time, but it reached the right ventricle below the blocked area, and the form of the resulting ventricular complex is more nearly normal than that of the sequential ventricular complexes.

In a case published by one of us in 1915,[14] transitions were obtained between the normal complexes and complexes characteristic of right bundle branch block. These transitional complexes must have been due to delayed conduction through the right branch of the His bundle (Fig. 20). From the analysis of a large number of transitions (obtained in Lead III) it was found that changes in the QRS group and in T usually appeared simultaneously. The most constant feature of the transitional complexes was their diphasic character, which was usually evident even in those nearest the normal complexes. The transitional complexes differed from the fully developed bundle branch block complexes principally in their lesser amplitude. As one proceeds from the first abnormal complexes of Figure 20 toward those typical of bundle branch block the amplitudes of QRS and T gradually increase and as these two deflections are in opposite directions the diphasic character of the complexes is gradually accentuated.

The clinical evidence, therefore, is in accord with the experimental evidence that diphasic ventricular complexes are often produced by delayed conduction through the branches of the His bundle.

As to the question of recognizing bundle branch block: It has been pointed out that only a small percentage of the aberrant ventricular

14. Wilson, F. N.: A Case in Which the Vagus Influenced the Form of the Ventricular Complex of the Electrocardiogram, Arch. Int. Med. **16**:108 (July) 1915.
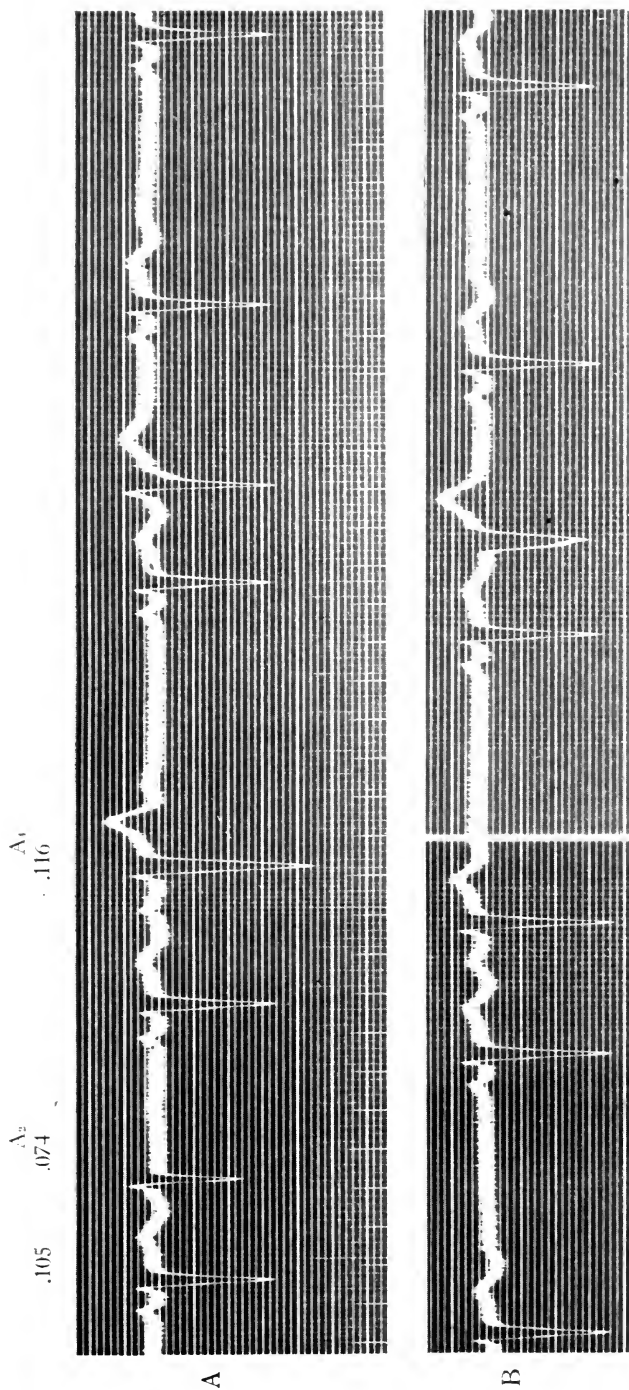
Fig. 19.—Same patient as Figure 18. Lead III. QRS interval of sequential beats 0.105. QRS of interpolated ventricular extrasystole (cycle A_2) 0.074. QRS of auricular extrasystole (cycle A_3) 0.116.
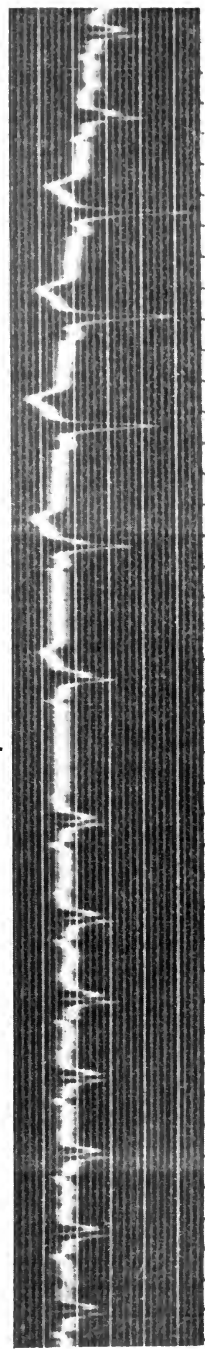
Fig. 20. Transition from complexes of normal type to complexes characteristic of right bundle branch block (Lead III). Transitional complexes diphasic and of smaller amplitude than bundle branch block complexes.

complexes observed clinically are typical examples of this condition. What are the others? It seems probable that some of them, especially those which show a very long QRS interval, are atypical examples of bundle branch block. There is a great deal of variation in the normal complexes of different individuals due to many causes; variations in the position of the heart; variations in the distribution of the ventricular muscle, and variations in the architecture of the Purkinje system. All of these causes tend also to bring about variations in the ventricular complex of bundle branch block. In addition we are dealing in the case of clinical bundle branch block with pathologic hearts which show much greater variations in the distribution of muscle mass and in position than the hearts of normal individuals. Great variations in the form of the ventricular complex of bundle branch block in man are, therefore, to be expected.

In addition to complete bundle branch block we may have incomplete bundle branch block or what is more properly termed delayed conduction through one of the main branches of the His bundle. We have given clinical and experimental evidence indicating that this may explain many of those aberrant ventricular complexes which are diphasic and which show an increased QRS interval. It is important to note that aberrant complexes of this type are more often of the form to be expected from delayed right than of the form to be expected from delayed left branch conduction; a fact which fits in well with the greater frequency of complete bundle branch block on the right than on the left side.

ARBORIZATION BLOCK

Oppenheimer and Rothschild [15] recently reported a series of cases in which aberrant electrocardiograms were obtained and in which the pathologic findings indicated that lesions of the smaller subdivisions of the His bundle and their arborizations were present. They believe that the abnormality of the ventricular complexes in these cases was due to defective conduction through the finer branches of the ventricular conducting system, and used the term arborization block to indicate this disturbance. The following criteria were given for the recognition of this condition.

1. Abnormal prolongation of the time interval of the QRS group beyond the normal limit of 0.1 second. This prolongation is most manifest in a widening of the R wave so that its foot points are abnormally separated. The R wave no longer has its slender tall spike-like appearance, but is broader and sometimes blunter than normally.

15. Oppenheimer, B. S., and Rothschild, M. A.: Electrocardiographic Changes Associated with Myocardial Involvement, J. A. M. A. **69**:429 (Aug. 11) 1917.

2. Notching of the R wave. This notching may appear on the ascending limb, on both limbs or at the peak. It may be multiple, and its degree and location may vary slightly from beat to beat. In arrhythmias, the shorter the preceding interventricular interval, the more pronounced is the evidence of disturbed intraventricular conduction.

3. Low voltage as expressed by a low amplitude of the waves in all three leads. This change is not uniformly present but when it occurs it helps to differentiate this type from the electrocardiograms of typical bundle branch block.

4. Absence of typical diphasic curves with huge T waves found in experimental bundle branch block.

The pathologic findings need not be described in detail; they included coronary arteriosclerosis with occlusion of the anterior descending branch of the left coronary artery and patchy sclerosis involving mainly the subendocardial muscle and Purkinje tissue. The changes were grossly more marked in the left ventricle than in the right.

EXPERIMENTAL LESIONS OF THE SMALLER SUBDIVISIONS OF THE HIS
BUNDLE AND THEIR EFFECT ON THE FORM OF
THE ELECTROCARDIOGRAM

By the term arborization block, Oppenheimer and Rothschild refer to defective conduction beyond the subdivision of the two chief branches of the His bundle. The experimental evidence bearing on this problem is of interest. In attempts to cut the left branch of the His bundle which spreads out fanwise over the left surface of the septum many experiments are failures, for it is rarely possible to cut the left branch before it subdivides. In many instances the cut transects only a portion of the fan. Eppinger and Rothberger publish one curve from such an experiment. It is definitely abnormal and of unusual form; on vagus stimulation typical left bundle branch block resulted. It was found that the cut had transected the posterior limb of the fan and had slightly injured the anterior limb. Hemorrhage into the uncut portion of the bundle was apparently responsible for the complete bundle branch block which ensued coincidentally with vagus stimulation. This experiment does not necessarily indicate that section of the posterior limb of the left branch produces profound changes in the form of the ventricular complex, for the anterior limb was also injured and the curves obtained may be interpreted as being due to delayed conduction through the left branch as a whole. Lewis does not mention the effect of cutting the subdivisions of the left branch; but in the paper written with Rothschild,[10] the statement is made that section of that portion of the right branch which bridges the ventricular cavity in the dog produces a diminution of R and an increase of S in the axial electrocardiogram. We have cut minor subdivisions of the left branch in many, and major subdivisions of

the left branch in a few instances, and we have in one instance cut all those subdivisions of the right branch which bridge the ventricular cavity, and we have never observed more than slight changes in the form of the electrocardiogram as a result of these lesions. Such changes as did occur did not resemble, in any way, the changes believed to result from so-called arborization block. There is, therefore, no evidence yet available to show that experimental lesions of the larger subdivisions of the branches of the His bundle produce more than minor changes in the form of the electrocardiogram. Nor would striking changes be expected for the subdivisions of the branches of the His bundle anastomose very freely,[10] and it is difficult to see how any lesion of these structures, except an extremely extensive one, could greatly delay the passage of the excitation wave over the ventricular muscle or could greatly change its course.

The effect of diffuse lesions involving large areas of the Purkinje network is a different matter. The only experiments bearing on this problem are those published by Lewis and Rothschild.[10] They showed that a cut completely transecting the endocardial surface of the conus region may delay the activation of the conus muscle by as much as 0.02 second. The delay is comparatively slight; the region chosen is a particularly favorable one for the purpose, for the cut can be so made as to transect all or nearly all of the Purkinje plexus supplying the conus muscle. The experiments indicate that the excitation wave travels through the Purkinje system more rapidly than through the ordinary ventricular muscle. They do not necessarily indicate that patchy lesions of the subendocardial tissues, such as Oppenheimer and Rothschild describe, may produce striking changes in the form of the ventricular complex.

It should be noted that Smith,[16] who did a large number of experiments in which he ligated various branches of the coronary arteries, obtained extensive lesions of the subendocardial tissues, but did not observe abnormalities of the electrocardiogram similar to those attributed to such lesions by Oppenheimer and Rothschild.

In conclusion, it must be admitted that there is little experimental evidence to indicate that lesions of the subdivisions of the branches of the His bundle or their arborizations produce striking or characteristic changes in the form of the electrocardiogram. Until such evidence is brought forward the diagnosis of arborization block rests on a very insecure foundation.

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16. Smith, F. M.: The Ligation of the Coronary Arteries with Electrocardiographic Study, Arch. Int. Med. **22**:8, 1918.

SUMMARY

Complete bundle branch block produces characteristic changes in the form of the ventricular complex both in animals and in man.

Delayed conduction of the impulse through the branches of the His bundle (incomplete bundle branch block) produces ventricular complexes which are transitional in form between the normal ventricular complex and complexes characteristic of complete bundle branch block.

The T deflection is produced by the deactivation of the ventricular muscle. In Lead II of the dog the upstroke of T in right bundle branch block is mainly a left ventricular effect; the downstroke of T in left bundle branch block is mainly a right ventricular effect.

There is little experimental evidence to indicate that lesions of the subdivisions of the branches of the His bundle or their arborizations produce those changes in the form of the ventricular complex usually attributed to arborization block. Until such evidence is brought forward the diagnosis of arborization block rests on an insecure foundation.

A CASE EXHIBITING SLOW AURICULOVENTRICULAR RHYTHM AND PAROXYSMAL TACHYCARDIA WITH UNUSUAL ABILITY TO INTERRUPT THE FAST RATE *

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PHILADELPHIA

INTRODUCTION

Tracings from clinical cases exhibiting auriculoventricular rhythm are comparatively rare, although the reports of Belski,[1] Cowan, Fleming and Kennedy,[2] and Hume[3] suggest that the condition is not uncommon, at least as a transient manifestation, in certain more or less acute diseases that especially attack the heart, such as diphtheria, rheumatic fever and subacute endocarditis. It is undoubtedly rare in chronic cardiac disease, and is usually, but apparently not always, associated with extensive myocardial involvement. It may also be produced experimentally in normal persons by various disturbances of the inhibitory apparatus.

Englemann[4] was the first to recognize auriculoventricular rhythm, following his application of the first Stannius ligature in the frog. Lohmann[5] obtained the rhythm in the mammalian heart. Since that time, a large amount of experimental work has been done, culminating in the studies of Meek and Eyster,[6] who proved the actual auriculoventricular nodal origin of the rhythm by the method of initial negativity. These investigators, working on dogs, concluded that the inherent automaticity of the auriculoventricular node, although subject to wide individual variations, averaged about two-thirds that of the sinus node; when impulses did not arrive from above at a more rapid rate than they were being formed at the auriculoventricular node, the latter tended to assume the cardiac autonomy.

Experimentally produced auriculoventricular rhythm may be classified into two types, according to the method by production. Type I, which has been most studied, is produced by depression or abolition

1. Belski: Ztschr. f. klin. Med. **67**:67, 1909.
2. Cowan, Fleming and Kennedy: Lancet **1**:227, 1912.
3. Hume: Heart **5**:25, 1913.
4. Engelmann: Arch. f. Anat. u. Physiol., Phys. Abth., p. 505, 1903.
5. Lohmann: Ibid., p. 431, 1904.
6. Meek and Eyster: Heart **5**:227, 1914; Arch. Int. Med. **18**:775 (Dec.) 1916.

of automaticity at the sinus node, or interference with conduction of impulses to the auriculoventricular node. Consequently, it is a relatively slow rhythm. Type II, brought on by exaltation of automaticity of the auriculoventricular node, was first produced by Rothberger and Winterberg [7] by stimulation of the left accelerator nerve. It is, therefore, relatively more rapid than sinus rhythm.

The above mentioned types of experimentally produced auriculoventricular rhythm, according to Lewis' [8] classification, are of the ectopic hemogenetic type. Most of the clinical cases are also of this type. The majority are due to depressive influences exerted above the auriculoventricular node, although some are doubtless aided in their production by the effect of accelerator influences on the node. As far as we are aware, no clinical case of the homogenetic type has been demonstrated to be due solely to acceleration of auriculoventricular stimulus production, although the work of Rothberger and Winterberg would seem to show that such a case would be theoretically possible.

The paroxysmal junctional tachycardias, although ectopic heterogenetic rhythms and consequently of fundamentally different character, are also classified as auriculoventricular rhythms. This group is rare, eight probable cases being reported. The characteristics of paroxysmal tachycardia distinguish them from homogenetic rhythms, but it has been impossible to differentiate absolutely some of the cases of functional origin from paroxysmal auricular tachycardia with delayed conduction, as in Lewis' [9] second case. Lewis' [10] first case and Cohn's [11] case, however, appear to be clear-cut and establish the condition as an entity.

The case we wish to report shows the following features of interest:

1. The length of time shifting of pacemaker back and forth between the sinus and auriculoventricular nodes was observed.

2. The variations in rate during auriculoventricular rhythm.

3. Alterations in As-Vs relations.

4. Attacks of paroxysmal tachycardia with unusual ability on the part of the patient to interrupt the fast rate.

5. The unusual behavior of the heart following the interruption of the tachycardia.

6. The resemblance of the tracings of the tachycardia, in a case which had previously shown auriculoventricular rhythm, to those of paroxysmal junctional tachycardia.

7. Rothberger and Winterberg: Arch. f. d. ges. Physiol. **135**:559, 1910.
8. Lewis: Quart. J. Med. **6**:221, 1913.
9. Lewis: Heart **2**:127, 1910.
10. Lewis: Heart **1**:306, 1910.
11. Cohn: Heart **2**:170, 1910.

REPORT OF CASE

Mrs. F. R., aged 62, was seen Dec. 21, 1919, at the Hospital of the University of Pennsylvania.

Present Complaint.—Palpitation of heart. The patient states that she has had attacks of palpitation of the heart since childhood. At that time she would get attacks of rapid heart beating after severe exertion. These attacks lasted a few minutes and disappeared quickly. She nevertheless took part in the ordinary plays of childhood. Gradually these attacks of palpitation increased. For the past two years she has been practically invalided.

The attacks begin often by clutching in the throat which she says last two days. Occasionally this would arouse her out of sleep, and at that time she would have sudden palpitation. This sudden palpitation makes her faint if she attempts to rise. Occasionally she has blackness before her eyes. From the very first of these very severe attacks of cardiac palpitation, the action could be controlled if she would hold her breath for a considerable length of time. When they could not be so controlled, when they ended they would end suddenly just as suddenly as they began. Occasionally, preceding an attack, she would have dimness of vision. Sometimes the attacks would come on after walking, sometimes as has been said, in her sleep. She has had slight swelling of her legs. Vertigo rather constantly, and vertigo always accompanies the severe cardiac distress. She has shortness of breath on the least exertion lately. Within the past six months she has been considerably worse and came to the hospital for rest. She has some aching in the region of her heart but no distinct pain. If an attack of palpitation of the heart came on while she was walking, she could usually reach home from a moderate distance, but with difficulty.

Physical Examination.—The eyes are entirely normal. There is no arcus senilis. There is slight edema of the skin over the body. Nothing abnormal is noticed about the ears. There was no glandular enlargement. She had some capped teeth, but apparently the teeth in general are in good condition. Her neck and throat are normal. The chest is normal in shape. She is spare for a woman of her general size. There is marked pulsation of the vessels of the arms and neck. Expansion of chest is normal. Abdomen is normal in shape.

The cardiac impulse is feeble. The apex beat is best felt just inside of the nipple line. Dulness of the heart is at the right edge of the sternum, at the upper border of the third rib and midclavicular line. There is a loud systolic murmur over the aorta and sternum, and also over the region of the apex. This murmur is conducted into the axilla. During this examination there is no arrhythmia. The first sound is almost entirely replaced by the murmur. Second is not unduly accentuated. The lungs are entirely normal and abdominal examination is entirely normal. At this first examination her heart was beating at about 50 a minute and was perfectly regular. Jan. 6, 1920, she was seen in an attack of tachycardiaa. The cardiac impulse was diffuse, but the dulness was apparently not increased. On auscultation, the heart's action was regular, the murmur which was loud during the slow action of the heart was difficult to hear. She was asked to hold her breath, which she did, and immediately after one or two attempts of interruption of the rhythm, the heart slowed down and continued at the rate of about 50 a minute while the examiner was in the room.

All of the laboratory tests were normal.

Apparently, the case was one of ordinary paroxysmal tachycardia in a heart which acted slowly between the paroxysms. Again, there was the unusual ability for her to control the attack of paroxysmal tachycardia by holding her breath, and the time between the first slow beats seemed unusually long, as though some block were occurring.

Fig. 1 A.—Lead III. Taken Jan. 24, 1920. First eight cycles. Auriculoventricular rhythm, rate about 60. No P wave visible. Spontaneous short period of sinus rhythm. Only slight conductivity defect; the P-R interval does not exceed 0.20 second. Slow auriculoventricular rhythm following sinus rhythm. Patient had received atropin sulphate, 1/100 grain, eight times in the preceding forty-eight hours and showed physiologic effects.
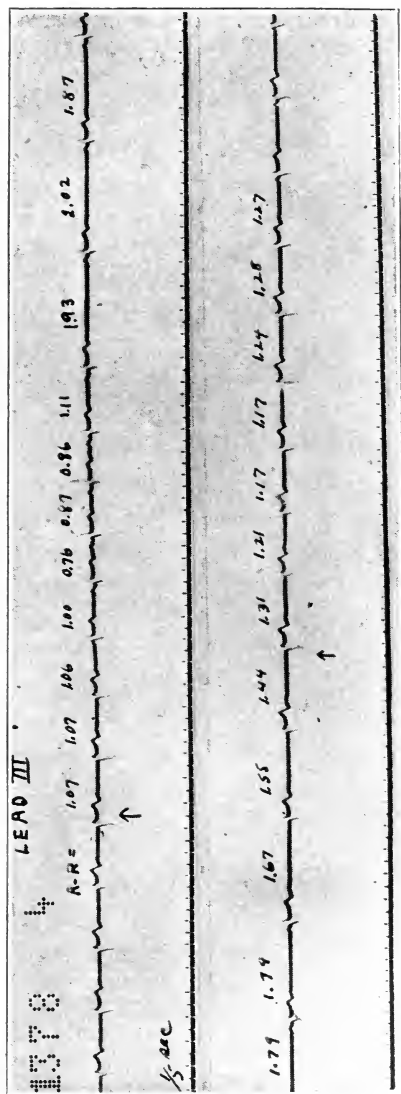

Fig. 1 B.—Lead III. Taken immediately after Fig. 1 A. Deep breath at point indicated by first arrow, held until point indicated by second arrow. Alteration in ventricular complex while breath was held. This tracing shows the typical variations in rate of the auriculoventricular rhythm and their relations to a period of sinus rhythm.

After about two weeks' rest in bed, the heart slowed down and the patient left the hospital January 31, very much more comfortable. She had not had an attack of tachycardia for two weeks.

She went from Philadelphia to Montrose in a comfortable car, developed a severe distressing cough with fever, and in about a week began to manifest signs of cardiac decompensation. She was seen in Montrose with a typical attack of decompensation, the heart beating about 160, dyspnea, large liver, edema of the lungs, and finally death occurred in two weeks after the beginning of this condition. No necropsy was held.

OBSERVATIONS ON THE SLOW AURICULOVENTRICULAR RHYTHM

Tendency for the Rhythm to Alternate Between the Sinus Node and the Auriculoventricular Node.—During the entire period of four weeks, while electrocardiographic studies were being made, a constant shifting of the pacemaker back and forth between the sinus and auriculoventricular nodes was observed, except during the periods of tachycardia. Tracings show from two to twenty cycles of normal rhythm, followed by transition to the slow rhythm, then abrupt change to the normal rhythm again. The periods of auriculoventricular rhythm observed varied from about thirty seconds to at least several minutes. Absolute rest and quiet favored longer periods of slow rhythm. Mild excitement, such as caused by applying electrodes, increased the frequency of periods of normal rhythm. Pressure on the vagi or ocular pressure sometimes cause shifting of the pacemaker back to the sinus node, but the results were inconstant. Once, a slight cough was followed instantly by return of normal rhythm, sometimes deep breathing produced the same result. Under varying amounts of atropin, the tendency for the pacemaker to shift spontaneously was not abolished.[12]

Variations in Rate During Auriculoventricular Rhythm.—The transition to auriculoventricular rhythm was sometimes preceded by a slowing of the sinus rhythm (Figs. 1 A and 1 B), sometimes it came on following an auricular extrasystole (Fig. 2 A), but frequently it occurred abruptly (Fig. 2 B) without preceding slowing of the sinus rhythm or extrasystoles. As a rule, after two or three cycles with increasing R-R intervals, the rate reached from 30 to 45, and with minor variations it tended to increase gradually, until eventually it became fairly steady around from 50 to 60, until the onset of the next period of sinus rhythm.

Owing to the spontaneous variations in rhythm, the case was not favorable for study of changes due to vagal influences. Pressure on the neck, ocular pressure and deep breathing produced no appreciable

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12. Atropin sulphate was administered by mouth, $\frac{1}{100}$ grain q. i. d., for one day, and t. i. d. the next four days. All statements in respect of atropin effects refer to observations made during this period.
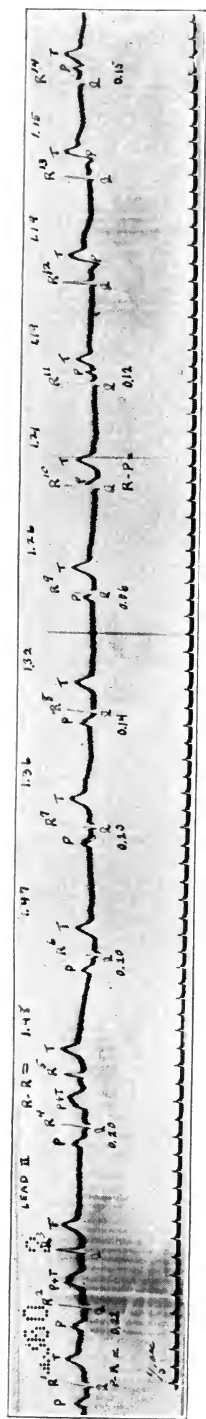
Fig. 2 A.—Lead II. Taken Jan, 2, 1920. First two cycles end a short period of sinus rhythm, followed by extra systole with delayed conduction. The beginning of auriculoventricular rhythm interrupted by another extrasystole. Gradual development of R-P sequence. Gradual acceleration of rate. (The patient had received tincture of digitalis, 10 minims by mouth the evening before and again on the morning this tracing was made.)
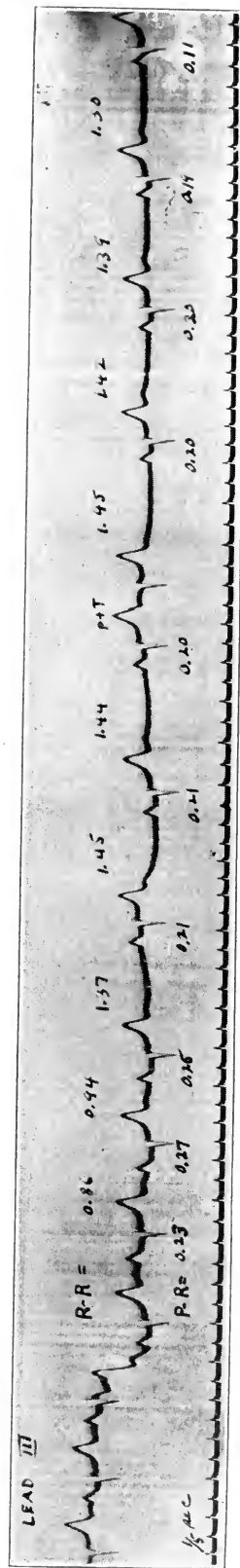

Fig. 2 B.—Lead III. Taken immediately after Figure 2 A. First seven cycles end a period of normal rhythm showing depressed conductivity. Abrupt onset of auriculoventricular rhythm. Gradually decreasing P-R intervals. Tendency toward acceleration of rate during auriculoventricular rhythm.

change except in so far as they sometimes initiated sinus rhythm. The atropin administration also was without effect apparently on the rate of the auriculoventricular rhythm.

The Relations of Auricular Systole to Ventricular Systole. — A slight depression of conductivity, which was not entirely abolished by atropin, was noted in all tracings, and at no time during sinus rhythm was the P-R interval less than 0.20 second. In Figure 2 it varies but reaches a maximum of 0.27 second. In connection with the onset of auriculoventricular rhythm, the P-R interval shows an immediate slight decrease. In general, after maintaining this relation for a few cycles, P gradually approaches R until it becomes lost in the Q R S group, sometimes emerging again to the left for a few cycles (Fig. 1 B, last cycle). The changes in P-R intervals occur usually in relation to changes in rate, the intervals decreasing toward zero as the rate increases. However, this relation is not constantly observed. Figure 2 A shows R-P intervals, and is the only tracing in which they were obtained.

Neither pressure on the vagi, ocular pressure, deep breathing nor the administration of atropin produced any appreciable changes in the relation of P to R.

OBSERVATIONS ON THE TACHYCARDIA AND THE INTERRUPTIONS PRODUCED BY THE PATIENT

The tracing shown in Figure 3 was taken during one of the paroxysms of tachycardia. The rate was about 135, the rhythm regular and the ventricular complexes, with minor differences in Lead II are similar to those occurring during sinus rhythm, except for the presence of the P wave between the Q R S group and the T wave.

For years the patient had been able to inhibit the tachycardia temporarily, and occasionally terminate an attack, by taking a deep breath and holding it. This maneuver was not always successful, but frequently a cycle of events, of which Figure 4 shows an example, occurred. After the breath was held for from ten to fifteen seconds, the tachycardia would terminate suddenly, sometimes with a moderately long pause followed by an isolated contraction, then an extremely long pause of from four to five seconds (Fig. 5 A), while sometimes the longest pause would occur immediately after the interruption of the tachycardia (Fig. 4). Following the long pause, contractions of supraventricular origin, but showing no evidence of P wave, occurred irregularly with single contractions or short runs of sinus origin interspersed. When the period of interruption lasted longer, a fairly regular slow auricular ventricular rhythm became established, inter-

rupted by short runs of sinus rhythm, similar in every way to the behavior of the heart observed apart from the paroxysms of tachycardia.

The position of the P wave with reference to the ventricular complex during offset and onset and during the period of interruption is
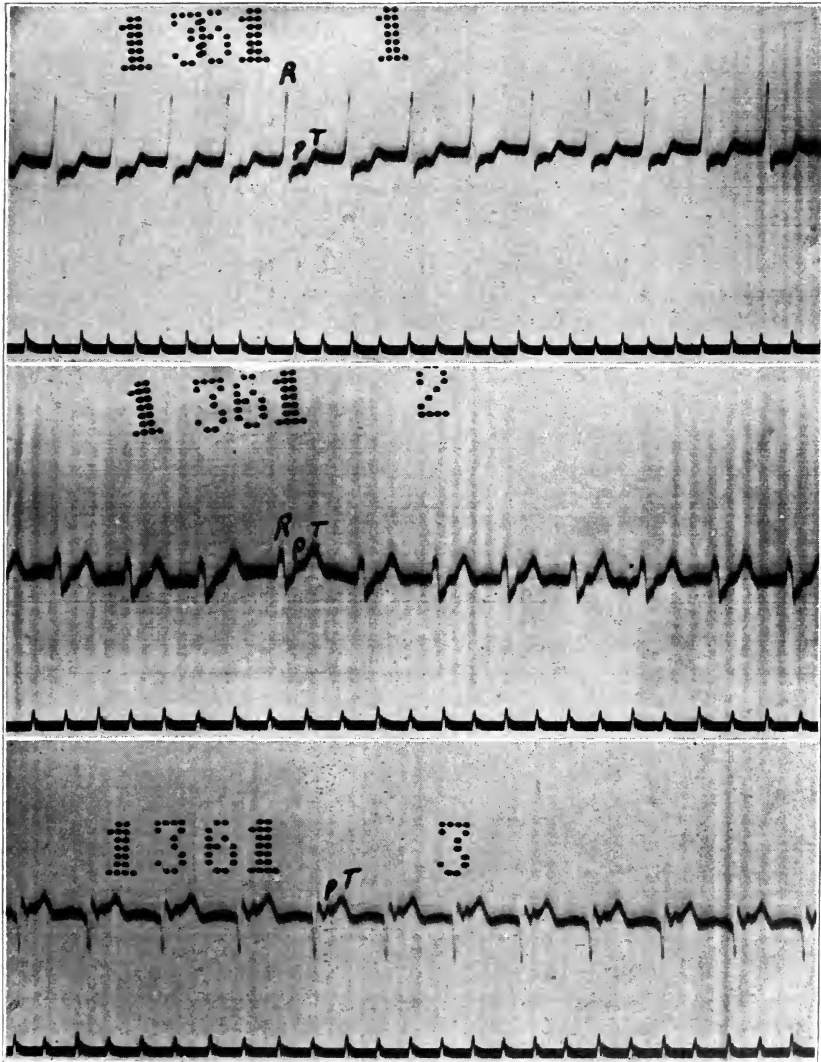

Fig. 3.—Taken Jan. 3, 1920. Shortly after the onset of the tachycardia. P wave between Q R S complex and T wave in all three leads.

of some interest. Figures 5 A and B show no evidence of auricular activity within the last ventricular complex before the offset. In Figure 5 A the first cycle after the offset has a P-R interval of 0.38

Fig. 4.—Lead III. Taken Jan. 7, 1920. Shows sequence of events following interruption of fast rhythm. Deep breath taken at point indicated by arrow. Held until patient was aware of changed rhythm. Long pause of 4.5 seconds followed by ventricular escape. No regular rhythm established. Long P-R interval at onset of tachycardia.
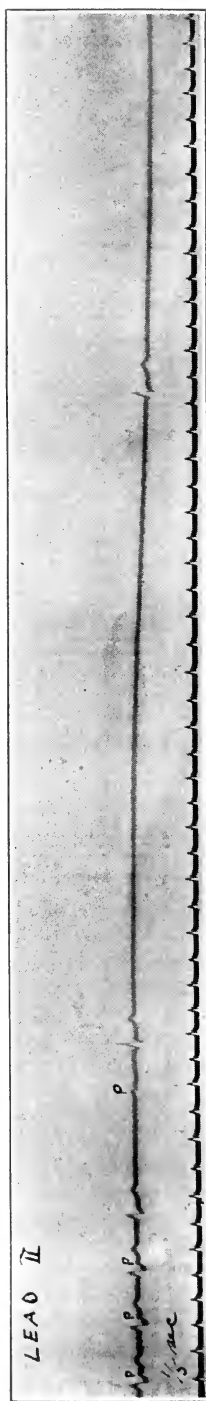
Fig. 5 A.—Lead II. Taken Jan. 5, 1920. Interruption of tachycardia. Last ventricular complex before offset does not show deformity due to P wave. Next contraction shows long P-R interval. The long pause lasts 4.9 seconds.
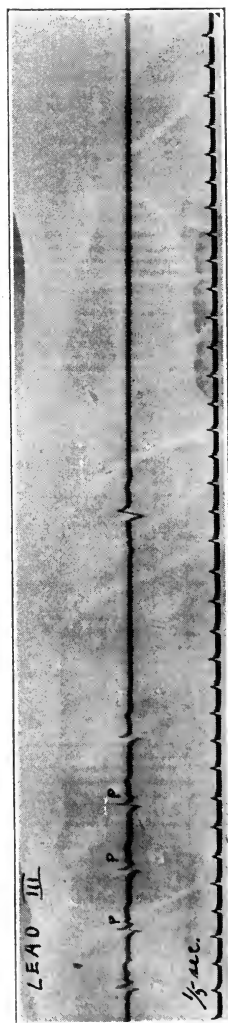
Fig. 5 B.—Lead III. Taken immediately after Figure 5 A. Interruption of tachycardia. Last ventricular complex does not show deformity due to P wave.

second. In Figure 4, during the interruption, the longest P-R interval observed in cycles of sinus origin is 0.28 second. The tachycardia is initiated again by a cycle with a P-R interval of 0.37 second.

<div align="center">COMMENT</div>

The Slow Rhythm.—While frequent alternations of the pacemaker back and forth between the sinus and auricular nodes has been observed in several cases, usually, as in those reported by Lewis [8] and Laslett,[13] the rates of stimulus production in the two centers are fairly close, so that Laslett's suggestion of variations in vagal tone as the determining factor in the shift, might well apply. In our case, attempts at stimulation of the inhibitory apparatus appeared to have some effect, but not a constant one, in bringing about a few cycles of sinus rhythm, or at least hastening the recurrence of such a period; however, the sinus rhythm would not persist whether the stimulation be continued or not. On the other hand, attempts to remove inhibitory control by atropin did not abolish the shifting back and forth of the pacemaker. The very slow rate following the sinus rhythm revealed the fact that the ability to produce stimuli in the sinus node must have been almost, if not completely, exhausted temporarily, and despite any nervous influences that could be brought to bear, required at least some rest to bring about a restoration of the function. The main effect of nervous influences was apparently to alter the length of the period before the node became able to discharge impulses again.

Changes in relation of auricular systole to ventricular systole during auriculoventricular rhythm have been studied experimentally by several observers. Hering [14] suggested that they were due to migration of the pacemaker. Zahn [15] and Meek and Eyster [6] demonstrated that migration of the pacemaker was accompanied by change in As-Vs intervals. According to the latter, coronary sinus rhythm was accompanied by only slight shortening of As-Vs time, but when the impulse arose in the lower or ventricular portion of the node, the ventricles might contract even before the auricles. Lewis, White and Meakins [16] have shown that reversed block might also account for changes in As-Vs relations during auriculoventricular rhythm, not only to the extent of producing Vs-As intervals, but to failure of transmission of impulse back to the auricles. White [17] was able to increase R-P intervals in his case by vagal stimulation and by digitalis, and to decrease the intervals lengthened by digitalis through

13. Laslett: Heart **6**:81, 1915.
14. Hering: Arch. f. d. ges. Physiol. **136**:446, 1910.
15. Zahn: Ibid. **151**:247, 1913.
16. Lewis, White and Meakins: Heart **5**:289, 1914.
17. White: Arch. Int. Med. **16**:517 (Oct.) 1915.

the administration of atropin. These effects were produced pre-
sumably by modifying reversed conduction. In those clinical cases
without depression of conductivity, spontaneously changing As-Vs
relations are probably dependent largely if not wholly on migration
of the pacemaker. Weil [18] ascribed the alterations in As-Vs relations
observed in his tracings to this factor.

In our case, the facts suggest that both migration of the pacemaker
and depressed conductivity are involved in the changing As-Vs rela-
tions, as seen in Figure 2 A and B. Explanation on the basis of inde-
pendent auricular and ventricular contractions falling near each other
is easily excluded, for even if it were granted that both auricles and
ventricles might be contracting at the same slow rate, it would be
unreasonable to expect them to maintain their relations in view of the
irregularities in rhythm that occur.

P-R intervals up to 0.27 second during the sinus rhythm, evidence
well marked depression of conductivity. The fact that P-R intervals
during the early cycles of auriculoventricular rhythm may still be
0.20-0.21 second (Fig. 2 A and B) demonstrates that the principal
defect in conductivity lies beyond the point of formation of impulses,
consequently a slight forward block is evident. But even complete
recovery of conductivity could not account for the development of the
R-P intervals. On the other hand, numerous tracings taken later,
when conductivity was improved, as in Figure 2, A and B, show not
only shorter P-R intervals at the beginning of the auriculoventricular
rhythm but no R-P relations at all. Consequently, the only explana-
tion that seems adequate to account for the facts observed is the
assumption that the region of the defect of conductivity is within the
auriculoventricular node; at the beginning of auricular rhythm, it lies
beyond the pacemaker and slight block is present; but by the migration
of the pacemaker to lower levels of the node, it is passed and slight
reversed block occurs.

The Tachycardia.—The tracings shown in Figure 3 admit of two
possible interpretations: (1) paroxysmal junctional tachycardia with
R-P intervals, or (2) paroxysmal auricular tachycardia with delayed
conduction. The explanation is furnished by the tracings showing
interruption and onset of the rhythm (Figs. 4 and 5, A and B). The
last ventricular complex before offset shows no P wave as it would
if the rhythm were of junctional origin, while the onset is initiated by
a cycle with a P-R interval of 0.37 second, demonstrating that con-
duction is delayed sufficiently for the auricular systole of a particular
cycle to fall within the ventricular systole of the preceding cycle
during the tachycardia.

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18. Weil: Deutsch. Arch. f. klin. Med. **116**:486, 1914.

The fact that conduction is so much more delayed during the tachy-cardia than occurred with sinus rhythm, is not to be explained in this case on the basis of depression of conductivity due to more frequent transmission of impulses. The first cycle of tachycardia shows the same marked delay in comparison with the contractions of sinus origin that occur just before it (Fig. 4). The same delayed con-duction is seen when auricular extrasystoles interrupt either sinus or auriculoventricular rhythm (Fig. 2, A and B). A possible explanation is furnished by the work of Eyster and Meek,[6] who show that conduc-tion from the sinus to the auriculoventricular node occurs normally not by spreading of the impulse through the mass of auricular tissue, but by specialized conduction paths; while conduction by the auricle may be accomplished, it is difficult and prolonged. Consequently, whether ectopic auricular impulses are carried to the auriculoven-tricular node through the mass of auricular tissue, or back to the sinus node and thence through the sinoventricular conduction paths the As-Vs time might be prolonged.

The mechanism by which the patient was able to interrupt the tachycardia was not clear. It has long been known that stimulation of the inhibitory apparatus may interrupt a paroxysm of tachycardia, but as shown in the case studied by Cohn and Fraser,[19] this usually occurs promptly. We were unable to initiate the change by pressure on either vagus or by ocular pressure. Carter and Wedd [20] exhibit tracings in which the tachycardia was thought to be interrupted by the aid of some voluntary effort on the part of the subject. In our case the fact that holding the breath for from ten to fifteen seconds at least, was necessary, raises the question as to whether slight asphyxial influences might temporarily depress the irritability of the ectopic focus in a heart with evident advanced myocardial disease and doubtless a precarious blood supply.

The unusual behavior of the heart following the interruption of the tachycardia, which, so far as we are aware, is unique, was prob-ably due, in part at least, to the easy exhaustion of stimulus produc-tion in the sinus node, which was pointed out above as the principal factor concerned in the shifting back and forth of the pacemaker during the periods of slow rhythm. Whether still further depression of the sinus node was caused by the same mechanism that depressed the irritable focus in the auricle could not be determined. Evidently, however, the automaticity of the auriculoventricular node was markedly disturbed and required time for its recovery so that a regular auriculo-ventricular rhythm could be established only during the longer periods of interruption of the tachycardia.

19. Cohn and Fraser: Heart **5**:93, 1913.
20. Carter and Wedd: Arch. Int. Med. **22**:571 (Nov.) 1918.

SUMMARY

A case is reported with a history of attacks of paroxysmal tachy-
cardia occurring over a period of more than forty years; an ability to
interrupt the fast rate with temporary cessation of cardiac activity;
periods of slow rhythm with interspersed short runs of about the
normal rate; abundant clinical evidences of myocardial disease and
decompensation.

The electrocardiographic tracings showed left ventricular pre-
ponderance, depressed conductivity, periods of sinus rhythm alternat-
ing with auriculoventricular rhythm, and paroxysmal auricular
tachycardia.

Observations were made in respect of the alternations of the
pacemaker between the sinus and auriculoventricular nodes, variations
in rate, relations of auricular systole to ventricular systole. The sig-
nificance of these phenomena is discussed.

The paroxysmal tachycardia was determined as auricular in origin
by analysis of curves of offset and onset. The method by which the
patient obtained interruption of the tachycardia is described, and an
attempt made to evaluate the factors responsible for the behavior of
the heart during the period of interruption.

EXPERIMENTAL OBSERVATIONS ON THE ATYPICAL Q-R-S WAVES OF THE ELECTROCARDIOGRAM OF THE DOG *

FRED M. SMITH, M.D.

CHICAGO

In the last few years considerable interest has been shown in the atypical Q-R-S waves of the electrocardiogram. These abnormal electrocardiograms have usually been seen in patients who gave clinical evidence of a failing myocardium. Many have died from cardiac failure within a few months following the time these abnormal electrocardiograms were discovered. In those cases that came to necropsy there has usually been found an extensive fibrosis of the heart which often involved the endocardial and subendocardial layers.

Until recently it was generally believed that these atypical Q-R-S waves were due to a lesion of one or the other of the main branches of the auriculoventricular bundle. This conception was based primarily on the experimental work of Eppinger and Rothberger.[1] They produced experimental lesions of the right and left branch of the auriculoventricular bundle. Those hearts with a lesion of the right branch gave an electrocardiogram in which the ventricular phase resembled that of a premature contraction rising in the base of the left ventricle. Those with lesions of the left branch caused ventricular waves similar to those of a premature contraction originating in the apex of the right ventricle. In the former instance the R-wave in Lead I and the S wave in Lead III are those encountered in preponderance of the left ventricle, while in the latter the S wave in Lead I and R wave in Lead III are those of hyperbalance of the right ventricle. Later Cohn and Lewis,[2] Mathewson[3] and also Carter[4] reported clinical electrocardiograms resembling those produced experimentally by Eppinger and Rothberger, accepting the interpretation of the latter investigators. In some instances, the patients came to necropsy, and histologic examination of the hearts showed lesions of the right branch of the auriculoventricular bundle.

1. Eppinger and Rothberger: Ztschr. f. klin. Med. **50**:1, 1910.

2. Cohn and Lewis: Heart **4**:15, 1912.

3. Mathewson: Heart **4**:385, 1913.

4. Carter, E. P.: Clinical Observations of Defective Conduction in the Branches of the Auriculoventricular Bundle. A Report of Twenty-Two Cases in Which Aberrant Beats Were Obtained, Arch. Int. Med. **13**:803 (June) 1914.

In 1917, Oppenheimer and Rothschild [5] reported a series of sixty-two cases with atypical Q-R-S waves. A careful histologic study was made in eleven hearts obtained from necropsies. They found a disseminated patchy sclerosis which in most instances involved the endocardial and subendocardial layers of the heart. They concluded that the abnormal electrocardiograms were due to lesions of the branching fibers of the auriculoventricular bundle, and suggested that the condition be known as "arborization block." Recently Carter,[6] Willius,[7] Neuhof [8] and Wedd [9] reported cases, accepting the interpretation suggested by Oppenheimer and Rothschild.

In 1916, Robinson [10] reported cases in which the broad and notched R waves of the electrocardiogram changed to the normal form while the patients were at rest and under the effects of digitalis. He suggested at this time that possibly fatigue of the heart muscle might be a big factor in the production of these abnormal ventricular waves. Later clinical observations,[11] the work of Fletcher and Hopkins [12] on the effect of diminished oxygen supply on muscle activity, and the experiments of Mines [13] and of Burridge [14] on the effect of change in hydrogen ion concentration on conduction through the ventricles, led Robinson to advance the hypothesis that these abnormal electrocardiograms were caused by an accumulation of acid metabolites in the ventricular structures.

The diversity of opinion as to the interpretation of these atypical waves has led to the investigation which forms the basis of this report. In this work the abnormal electrocardiograms under consideration were produced experimentally in the dog.

5. Oppenheimer, B. S., and Rothschild, M. A.: Electrocardiographic Changes Associated with Myocardial Involvement, J. A. M. A. **69**:429 (Aug. 11) 1917.

6. Carter, E. P.: Further Observations on the Aberrant Electrocardiogram Associated with Sclerosis of the Atrio-Ventricular Bundle Branches and Their Terminal Arborizations, Arch. Int. Med. **22**:331 (Sept.) 1918.

7. Willius, F. A.: Arborization Block, Arch. Int. Med. **23**:431 (March) 1919.

8. Neuhof, S.: The Clinical Significance of the Abnormally Wide Ventricular Deviation in the Electrocardiogram, Arch. Int. Med. **22**:45 (July) 1918.

9. Wedd, A. M.: The Clinical Significance of Slight Notching of the R-Wave of the Electrocardiogram, Arch. Int. Med. **23**:515 (April) 1919.

10. Robinson, G. C.: The Relation of Changes in the Form of the Ventricular Complex of the Electrocardiogram to Function Changes in the Heart. Arch. Int. Med. **18**:830 (Dec.) 1916.

11. Robinson, G. C.: The Significance of Abnormalities in the Form of the Electrocardiogram, Arch. Int. Med. **24**:422 (Sept.) 1919.

12. Fletcher and Hopkins: Lactic Acid in Amphibian Muscle, J. Physiol **35**:247, 1907.

13. Mines: On Dynamic Equilibrium in the Heart, J. Physiol. **46**:349 1913.

14. Burridge: Propagation of Contraction in the Frog's Heart, J. Physiol. **45**:6, 1912.

METHOD

The anesthesia, artificial respiration and the method of exposing the heart were the same as employed in former work.[15] Lesions of the branches of the auriculoventricular bundle were produced by incising the endocardium of the ventricles. A small knife with a long oval shank was adopted for this work. This knife was introduced into the ventricular cavity through the wall at a point nearly opposite that area of the endocardium that we wished to incise. That point of the cardiac wall to be pierced by the knife on introduction into the
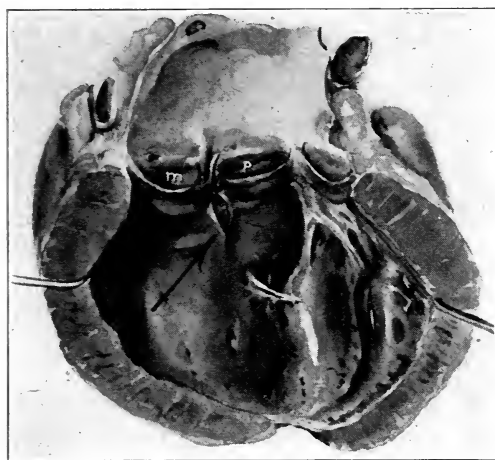
1

2

Fig. 1.—Dog 2. 1. The arrow points to an incision between the middle and posterior cusps of the aortic valves. The left branch of the auriculoventricular bundle was cut. The right branch soon failed to carry auricular impulses. See electrocardiogram, Figure 1. 2. Shows the point in the left ventricular wall through which the knife was introduced into the left ventricular cavity. This figure also shows the branches of the left coronary arteries that were ligated to hasten the dilatation of the left ventricle.

ventricular chambers was first enclosed by a purse-string suture. This suture was closed immediately following the withdrawal of the knife. Very little blood was lost from the ventricular chambers by this precaution. Electrocardiograms were taken prior to and at varying intervals following the incision of the endocardium.

15. Smith, F. M.: The Ligation of Coronary Arteries with Electrocardiographic Study, Arch. Int. Med. **22**:8 (May) 1918.

I. CASES IN WHICH BOTH BRANCHES OF THE AURICULOVENTRICULAR
BUNDLE WERE CUT

In four instances the interventricular septum was slit transversely just below the aortic valves. In two dogs the ventricles immediately assumed a much slower rhythm independent of that of the auricles. This slow rhythm did not develop in the third dog until a period of ten minutes had elapsed. In the fourth dog the ventricles immediately came to a standstill in diastole. They were stimulated to a slow rhythmical contraction by massage. In all instances the ventricles seemed to be laboring under great difficulty following the onset of the slow rhythm. The contraction wave, however, seemed normal. Within one hour the hearts of these four dogs became markedly dilated and cyanotic. The contractions of the ventricles at this time were distinctly modified. In some areas no contraction could be detected. Finally, both ventricles came to a standstill, except for a small area in the region of the interventricular septum. This condition was usually followed in a few minutes by ventricular fibrillation.

At necropsy, a transverse slit was found through the septum just below the aortic valves in three instances. Both branches of the auriculoventricular bundle had been cut. In the fourth dog a slit was found in the interventricular septum between the middle and posterior cusps of the aortic valves (Fig. 1). The left branch of the auriculoventricular bundle was cut and the right soon ceased to function, as shown by complete heart block that developed.

The electrocardiograms taken immediately following the incision of the septum showed some change in the Q-R-S group. The R wave was slightly broad at the base, and in one case notched. In one instance there was a broad and notched S wave. The T wave assumed the direction opposite to that of the R and S waves. The electrocardiogram became more abnormal as the ventricular contraction became more modified and the degree of heart block more pronounced (Fig. 2 [3]). The most atypical electrocardiograms were obtained at that time when the contraction of the ventricles was confined to the vicinity of the interventricular septum (Fig. 2 [4 and 5]).

II. CASES IN WHICH INCISIONS WERE MADE IN THE ENDOCARDIUM
OF THE LEFT VENTRICLE

In eleven instances, the endocardium of the left ventricle was incised. The contraction of this chamber was apparently not affected until dilatation was produced by ligation of the branches of the left coronary artery. In three cases the left ventricle dilated without our having ligated coronary arteries. These were instances in which the incisions were extensive and involved the deeper layers of the muscu-
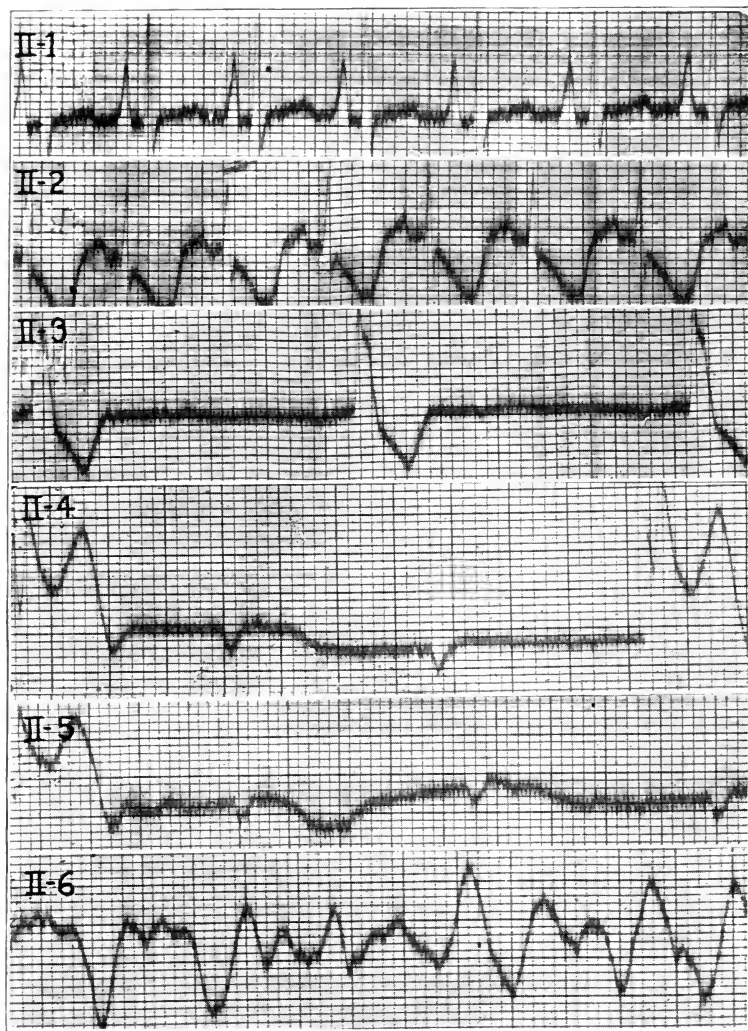
Fig. 2.—Dog 2. Lead II. 1. Initial electrocardiogram. 2. Record taken immediately after a slit was made in the interventricular septum between the posterior and median cusps of the aortic valves as shown in Figure 1. The T-wave is now a negative phase. 3. This electrocardiogram was taken after the onset of the slow rhythm—complete heart block. Note that the R-wave is notched and broad at the base. The heart had begun to dilate. 4. This electrocardiogram is even more abnormal. The ventricles were now markedly dilated and the contraction very atypical. 5. This record was taken as the condition of the heart was growing progressively worse. 6. Ventricular fibrillation.
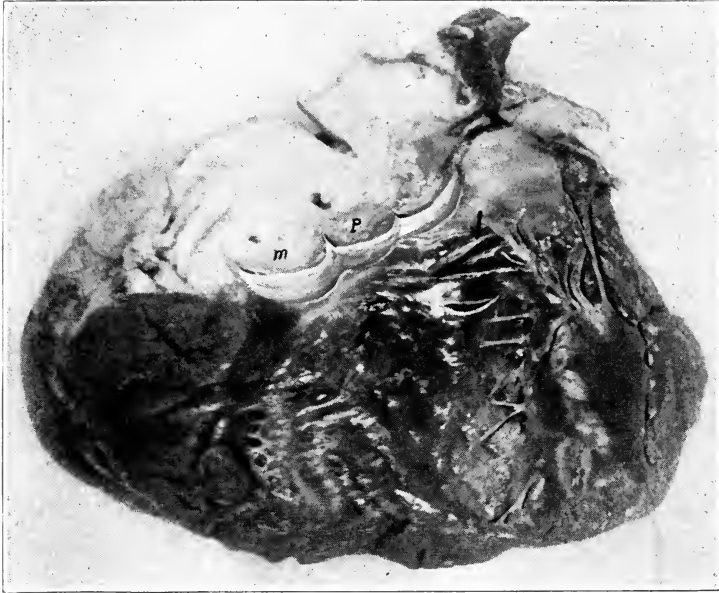
Fig. 3.—Dog 10. Arrows point to transverse incisions in the endocardium just below the aortic valves. See electrocardiogram, Figure 16.
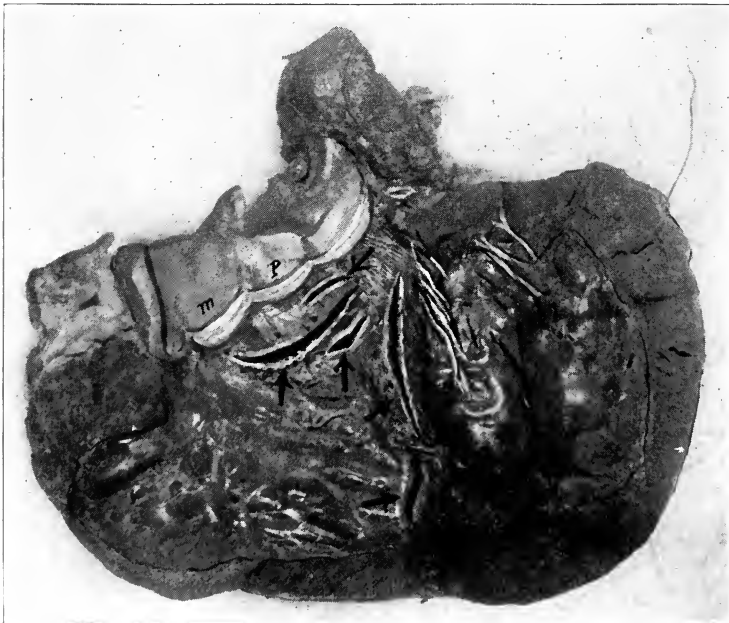
Fig. 4.—Dog 13. The arrows point to incision parallel and median to the posterior papillary muscle and also transverse incisions below the aortic valves. The largest of the latter incisions divided the left branch of the auriculoventricular bundle. See electrocardiograms, Figures 6 to 10.
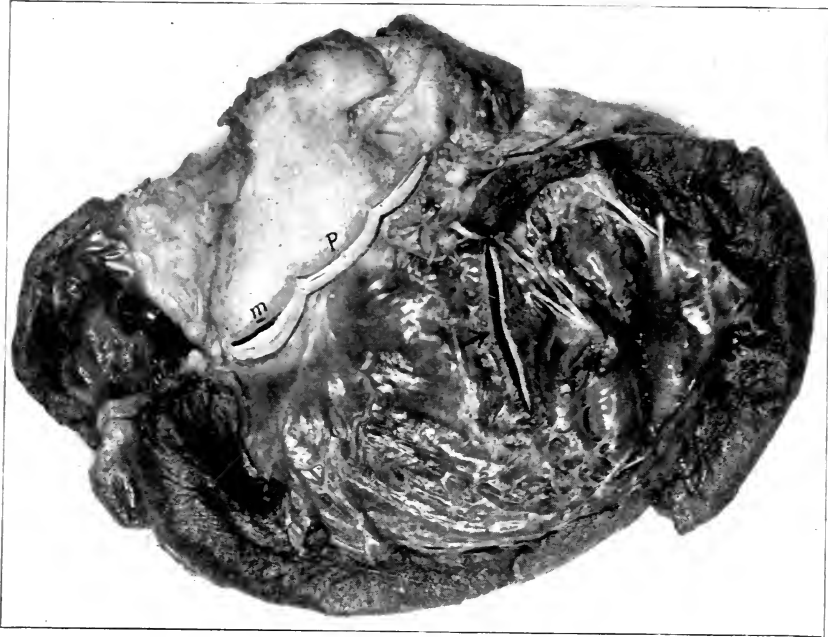
Fig. 5.—Dog 11. An incision in the endocardial and subendocardial layers parallel and median to the posterior papillary muscle. See electrocardiogram, Figure 11.
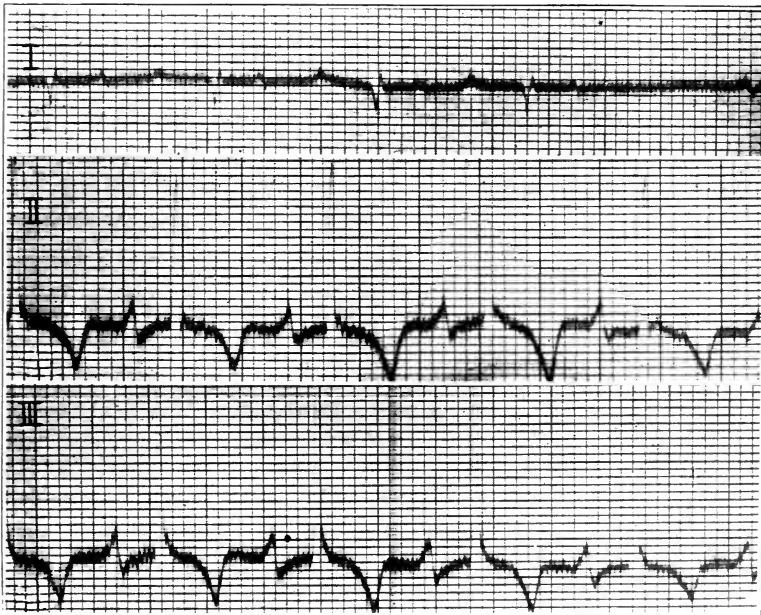
Fig. 6.—Dog 13. Initial electrocardiogram. The P-R interval is slightly prolonged.

lature. When the left ventricle became dilated and cyanotic, areas began to come to a standstill especially in the lateral and posterior basal regions. Later the contraction of both ventricles became limited to the vicinity of the interventricular septum as in those hearts in which both branches of the auriculoventricular bundle were cut.

At necropsy the incisions were found to vary as to extent and location. They were all located between the aortic valves and the posterior papillary muscle. In most instances there were two or more small transverse incisions just below the aortic valves (Figs. 3 and 4). Figure 4 shows in addition a long incision parallel to the posterior papillary muscle. In three cases there were incisions median and parallel to the posterior papillary muscle (Fig. 5).

Electrocardiograms taken immediately after extensive incisions had been made in the endocardium showed very little change in the Q-R-S group (Figs. 6, 7, 8 and 11 [2]). After the left ventricle became dilated and the contraction modified, the R wave was broad at the base and often notched (Figs. 9 and 11 [3]). Later this wave became more atypical (Fig. 11 [4 and 5]). In no instance was there an S wave in Lead I.

III. A CASE IN WHICH THE RIGHT BRANCH OF THE AURICULO-VENTRICULAR BUNDLE WAS CUT

In one instance the right branch of the auriculoventricular bundle was cut. The contraction of the right ventricle immediately became less than before the incision. In about twenty minutes this chamber stopped contracting except for a small area in the region of the interventricular septum. Later both ventricles became dilated and began fibrillating.

At necropsy, a longitudinal slit was found in the interventricular septum which extended up to the aortic valves (Fig. 12). Near the upper pole of this incision there was a communication between the ventricles that had been made by the knife. Although histologic examination was not made, it was impossible to see how the right branch of the auriculoventricular bundle escaped being cut.

The electrocardiogram taken immediately following the incision showed a prominent S wave in lead III (Fig. 14). This wave was slightly broad at the base, but not notched. This type of electrocardiogram is generally regarded as indicative of left ventricular preponderance. In this instance the preponderance of the left ventricle was due to a lessening of the contraction of the right ventricle. The electrocardiogram became more abnormal (Fig. 15) as the contraction of the right ventricle diminished and was most atypical just prior to the onset of ventricular fibrillation.
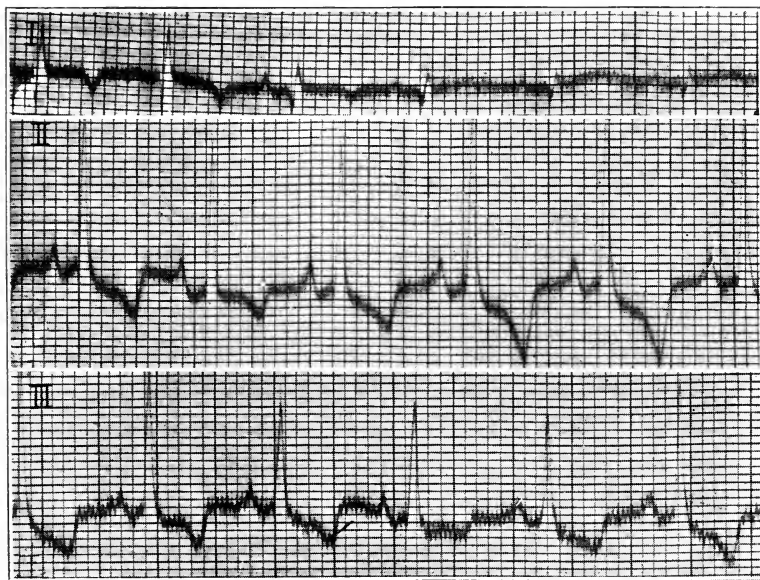
Fig. 7.—Dog 13. This record was taken immediately after an incision was made parallel and medial to the posterior papillary muscle as shown in Figure 4.
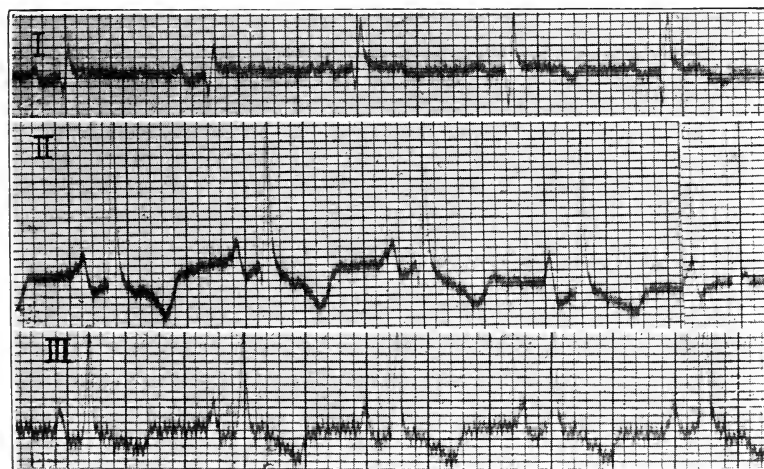
Figure 8.—Dog 13. This electrocardiogram was taken after that shown in Figure 7. There are no changes in the Q-R-S waves even though the conduction paths to the greater part of the left ventricles have been divided.
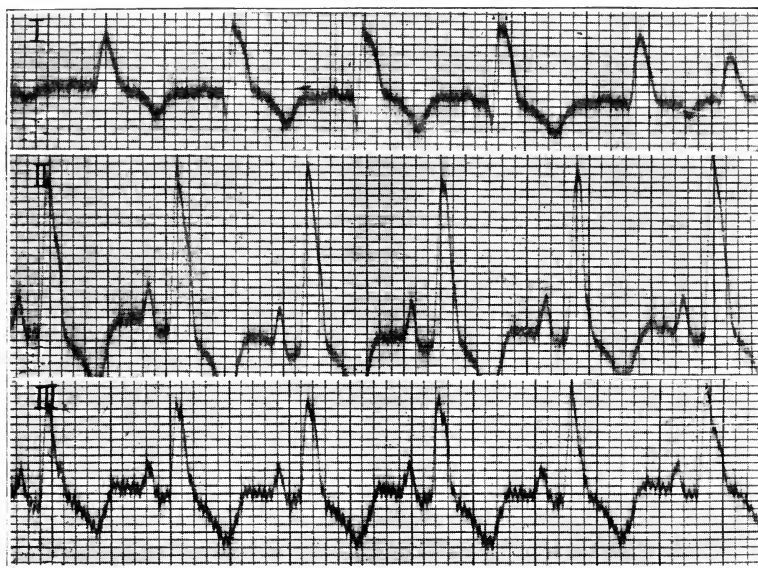
Fig. 9.—Dog 13. Electrocardiogram taken after the transverse incisions had been made in the endocardium below the aortic valves as shown in Figure 4. The heart was dilated at this time and there were areas in the posterior and lateral basal regions of the left ventricle in which there were no apparent contractions.
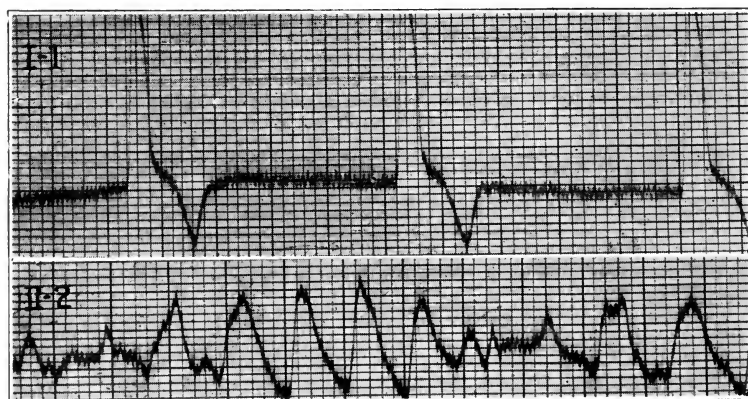
Fig. 10.—1. Dog 13. Lead II. This record was taken ten minutes following that shown in Figure 9. The auricles are now fibrillating. 2. This electrocardiogram was taken five minutes after that shown in 1 — ventricular fibrillation.

<div style="text-align:center">COMMENT</div>

There are reasons for believing that the "arborization block theory" advanced by Oppenheimer and Rothschild falls short of explaining the abnormal Q-R-S waves. In a former investigation [15] extensive fibrosis of the endocardial and subendodocardial layers of the heart of the dog was produced by the ligation of the coronary arteries. Many of these dogs were allowed to live for a period of two or three
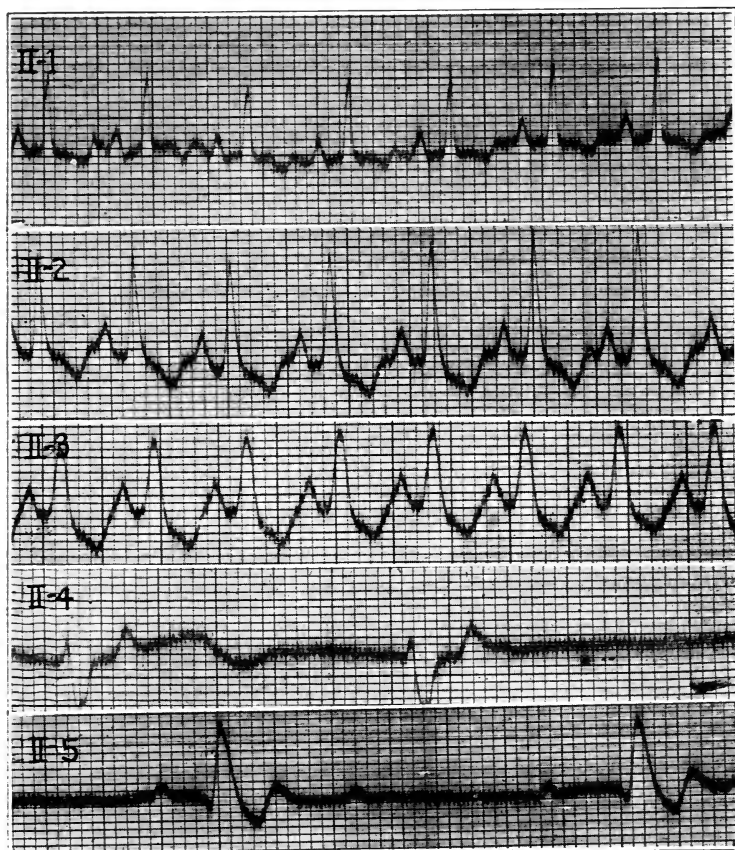
Fig. 11.—Dog 11. Lead II. 1. Initial electrocardiogram. 2. This record was taken twenty minutes after an incision was made in the endocardial and subendocardial layers median to and parallel to the posterior papillary muscle as shown by Figure 5. The R-wave is slightly broad at the base. 3. This record was taken fifteen minutes later. The R-wave is distinctly abnormal. The heart was dilated and the contractions of the left ventricle were very atypical. 4. This record shows auricular fibrillation and an abnormal S-wave. The contractions of the left ventricle were now even more atypical. 5. This electrocardiogram was taken just prior to the time the ventricles began fibrillating. Note the rhythmical contractions of the auricles and complete heart block. There is now a broad and blunt R-wave.

months.   During this time frequent electrocardiograms were taken.
In only one instance did they yield electrocardiograms resembling those
under discussion.

Herrick [16] recently reported a case of coronary occlusion which
came to necropsy.   An electrocardiogram taken of this patient a few
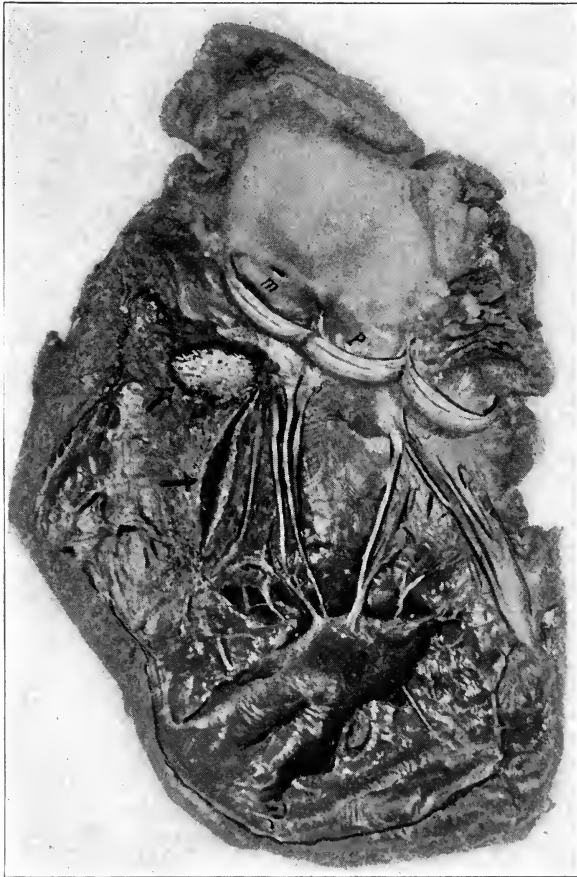
Fig. 12. — Dog 14.   Shows an incision in the long axis of the interven-
tricular septum which extends upward to the aortic valves.   The cotton near
the upper pole of this incision represents a traumatic communication between
the ventricles.   The right branch of the auriculoventricular bundle was
undoubtedly cut.   See electrocardiograms, Figures 13 to 15.

days prior to death was not of the type produced by the series of
cases reported by Robinson, Oppenheimer and Rothschild, Carter and
others.   It is hard to conceive how the intraventricular conduction
system escaped injury in the experimental hearts and in the clinical

16. Herrick, J. B.: Thrombosis of the Coronary Arteries, J. A. M. A. **72:**
387 (Feb. 8) 1919.
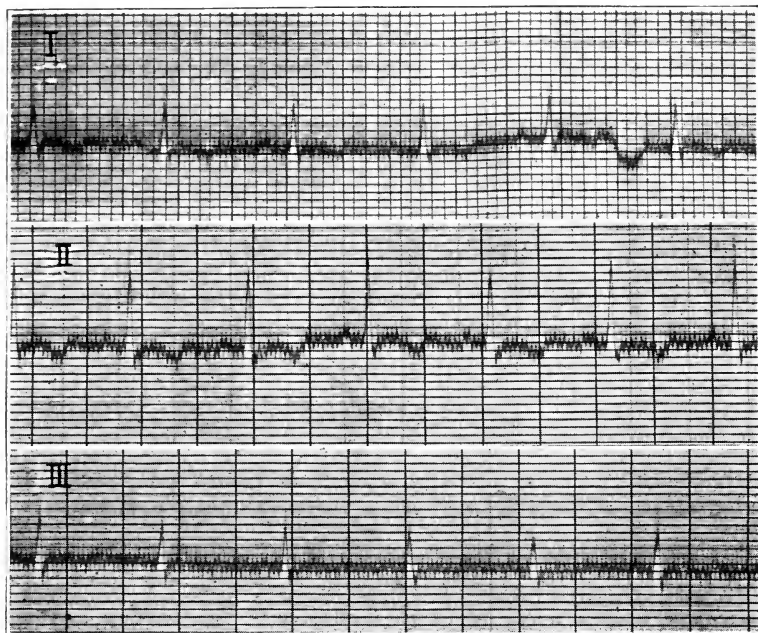
Fig. 13.—Dog 14. Initial electrocardiogram after heart was exposed.
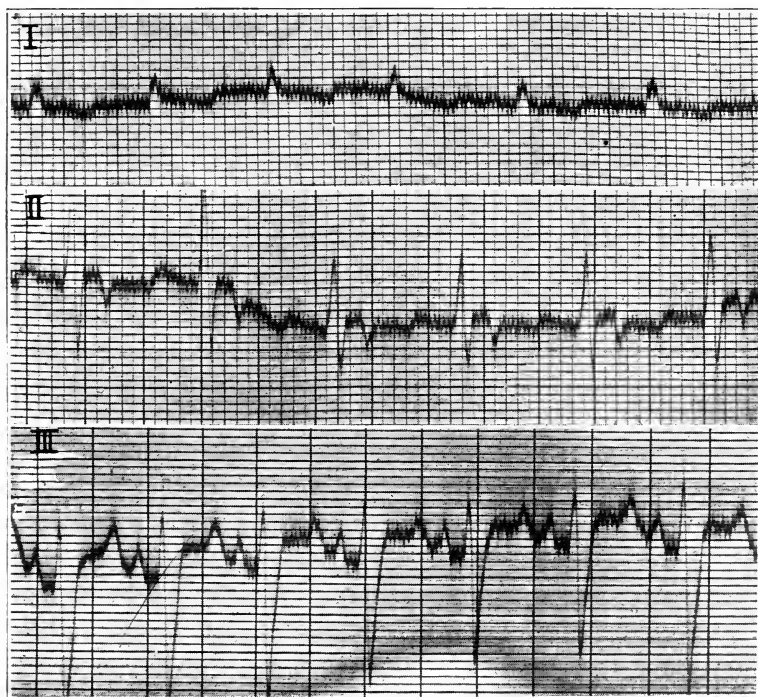
Fig. 14.—Dog 14. Electrocardiogram taken after a slit was made in the long axis of the interventricular septum (Fig. 12). There is a prominent S-wave in Lead III which is slightly broad at the base. This electrocardiogram indicates a preponderance of the left ventricle which in this instance is due to diminished contraction of the right ventricle.

case reported by Herrick with such an extensive fibrosis of the endo-cardial and subendocardial layers.

In the experiments covered by this report, normal electrocardio-grams were obtained from hearts in which there were extensive incisions which extended through the endocardial and even the sub-endocardial layers. Later, however, when the hearts became dilated and the contraction modified the electrocardiograms were always of the abnormal type.

Fatigue of the heart muscle seemed to be an important factor, but not alone responsible for the abnormal electrocardiograms in our experiments. Experiments were done in which the branches of the
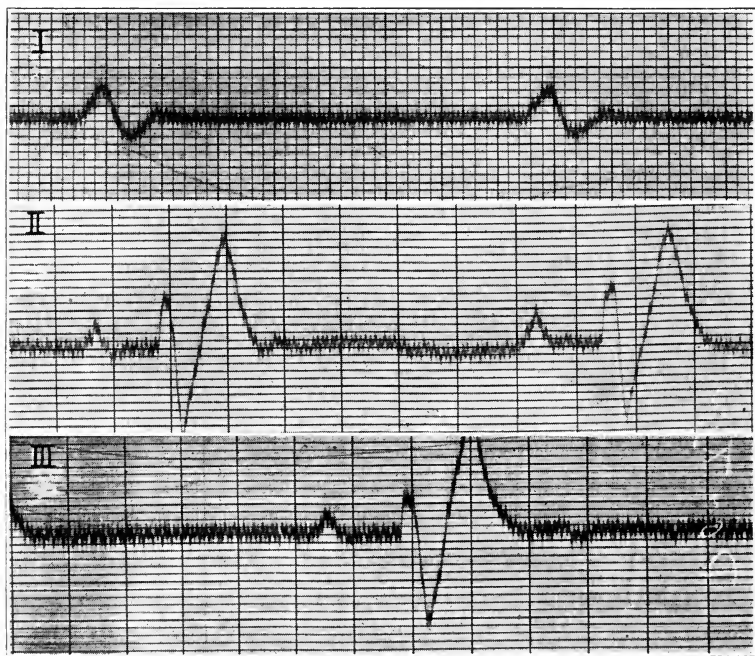
Fig. 15.—Dog 14. This electrocardiogram was taken at the time when the greater portion of the right ventricle was at a standstill and the contractions of the left ventricle atypical. Note the broad R- and S-waves. The P-R interval is increased.

coronary arteries were ligated and the heart forced to work in the partially closed hand of the experimenter until it became markedly dilated and finally went into ventricular fibrillation. Under these cir-cumstances the heart often worked for more than an hour with the greater part of the coronary blood supply cut off from one ventricle. According to Hopkins and Fletcher,[12] and also Mines,[13] the conditions were ideal for an accumulation of acid metabolites in the musculature.

In none of these experiments did the dog give electrocardiograms with abnormal Q-R-S waves. If, however, in addition an incision was made in the endocardium these waves became atypical.

These observations would seem to indicate that there are at least two factors necessary for the production of the type of electrocardiogram under consideration, lesions of the intraventricular condition system and cardiac fatigue. Cardiac fatigue alone did not produce the atypical electrocardiogram. When, however, a defect was also made in the intraventricular conduction system this abnormal type of
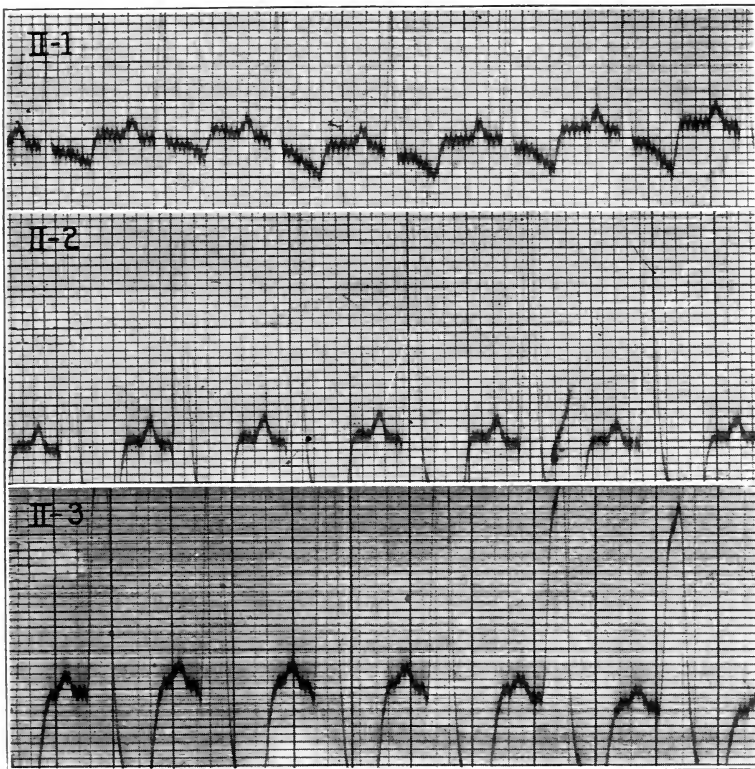
Fig. 16.—Dog 10. Lead II. 1. Initial electrocardiogram. 2. Record taken after transverse incisions were made in endocardium of left ventricle as shown by Figure 3. The height of the R-wave is increased and the base is slightly broad. The T-wave is more negative. The heart had begun to dilate. 3. Electrocardiogram taken after the ventricles had dilated and contractions become atypical. The R-wave is broad at the base and blunt at the peak.

electrocardiogram was always obtained. These results furnish a more satisfactory explanation of the abnormal Q-R-S waves of the clinical electrocardiogram. Patients are occasionally seen in whom these waves of the electrocardiogram become normal after rest and the adminis-

tration of digitalis. Some of these undoubtedly have permanent lesions of the intraventricular conduction system, as shown by Oppenheimer and Rothschild.[5] When, however, the physiologic processes of the heart are improved, the impulse may be able to reach all parts of the ventricles in normal time.

SUMMARY

A transverse slit was made in the interventricular septum just below the aortic valves in three dogs, cutting both branches of the auriculoventricular bundle. In one instance a short, shallow incision was made on the left ventricular side of the septum. In this case the left branch of the auriculoventricular bundle was divided. In one dog the right branch of the auriculoventricular bundle was divided by an incision in the long axis of the interventricular septum. In eleven dogs incisions were made in the endocardium of the left ventricle.

Electrocardiograms taken after one or both branches of the auriculoventricular bundle were divided showed some increase in the width of the R wave, and in some instances this wave was notched. In the one instance in which the right branch was cut there was an S wave in Lead III. Normal electrocardiograms were yielded by dogs in which there were extensive incisions in the endocardium of the left ventricle. Later as the ventricles became dilated and the contraction atypical the electrocardiograms became abnormal in all instances.

Cardiac fatigue alone was not responsible for the abnormal electrocardiograms in our experiments. Those hearts which were subjected to special strain by increasing the load and ligating the coronary arteries never produced an electrocardiogram with atypical Q-R-S waves. If, however, the endocardium of the left ventricle was incised these waves became abnormal. These experiments would seem to indicate that there are at least two factors necessary for the production of the abnormal electrocardiogram under consideration, lesions of the conduction system and cardiac fatigue.

GASTRIC POLYPOSIS (PAPILLOMATOSIS)

REPORT OF A CASE WITH OPERATION AND PRESUMABLE CURE *

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SAN FRANCISCO

Confirmed cases of gastric polyposis are comparatively unusual, although reports of isolated cases of the disease have appeared from time to time in the literature for many years. Balfour [1] pointed out that in approximately 69,000 abdominal sections in the Mayo Clinic, 8,000 of which were for gastric lesions, his case was the first one of gastric polyposis that had been encountered. I cannot believe that this represents the true incidence of the disease, and in studying histories of gastric cases, it seems entirely plausible that some of the vague and obscure conditions of the stomach, masquerading under such diagnoses as chronic gastritis, gastric neuroses, etc., might, on further investigation, prove to be benign tumor conditions of the gastric wall. Ebstein [2] found fourteen cases of stomach polyps in 600 necropsies, and was able to collect reports of eight others from the earlier literature. Novak [3] recently recalled that it is from the French that much of our knowledge of these growths has come. Cruveilhier [4] has the credit of reporting the first undoubted case of adenoma of the stomach in 1849, and it is from this specimen that Brissaud [5] made his comprehensive study of benign gastric neoplasms.

There are several varieties of primary benign tumors of the stomach. Basch [6] states that the term polypus is merely descriptive and not histologic, since adenomas, fibromas, lipomas, myomas and papillomas may all form polypoid tumors, in which, sometimes, the connective tissue predominates, at other times, the glandular elements. The same author enumerates and discusses the types of benign tumors which have occurred in the stomach, mentioning mucous polypi (of which there are the two anatomic types, first distinguished by Menetrier [7]), adenomas, lymphadenomas, myomas, fibromas, lipomas, myxomas, osteomas and cysts. The last seven of these are extremely

* From the Departments of Medicine and Surgery, University of California.

1. Balfour, D. C.: Surg., Gynec. & Obstet. **28**:465 (May) 1919.

2. Ebstein: Arch. f. Anat. u. Physiol., 1864.

3. Novak, E.: Polypoid Adenoma of the Stomach, J. A. M. A. **74**:871 (March 27) 1920.

4. Cruveilhier: Traité d'anatomie Pathologique, 1849, tome 2, livraison 30, 2,

5. Brissaud: Arch. gén. de méd. **2**:257, 1885.

6. Basch, S.: Surg., Gynec. & Obst. **22**:165 (Feb.) 1916.

7. Menetrier, P.: Des Polyadénomes gastriques et leurs rapportes avec de cancer de l'estomac, Arch. de Physiol. norm. et path. **45**:32, 236, 1888.

rare tumors, and only a few scattered examples of each have been found in the literature. It is, therefore, safe to assume that of the primary benign tumors of the stomach the polyadenomas and papillomas form the important groups clinically.

Menetrier's [7] anatomic classification of the gastric polypoid conditions is still accepted and seems useful. He distinguishes two varieties, depending on whether the ducts or the fundus of the gastric glands are involved. When the ducts are principally involved, the tumor is distinctly lobulated, and cysts are more common, owing to the obstruction of the excretory ducts. On the other hand, when the alteration is chiefly in the fundus, there is little or no lobulation, and the cysts are either few in number or entirely absent. In this latter type, the polyps have a more uniform appearance and tubulation is less pronounced. To the first type he gives the name "polyadenomes polypeux" and to the second "polyadenomes en nappe." This latter type appears to be a very rare condition, and up to 1913, Meyer [8] states that only three authentic cases have been reported, one of them by Andral and the other two by Menetrier. Hayem [9] described a third type of tumor which he calls the Brunnerian adenoma. The glands are of the duodenal type and are thought to have their "anlage" in misplaced duodenal glands. Anatomically, the case I report conforms to the rare variety of Menetrier, the "polyadenomes en nappe;" however, the histologic structure is not that of an adenoma but of a papilloma. This finding is in keeping with Basch's observation that polypoid conditions in the stomach result from numerous types of microscopic tumor patterns.

The object of this paper is, therefore, to put on record another of these unusual cases of benign gastric tumors, which in this instance proved to be a polyposis of a papillomatous histologic structure. The patient was first seen in September, 1919, when I was working in the Medical Out-Patient Department of the University of California. This patient was observed over a period of about one month. Finally, a diagnosis of gastric carcinoma was made, which was concurred in by the roentgen-ray department, and the patient was then admitted to the hospital on Dr. Wallace I. Terry's surgical service.

REPORT OF CASE

H. S., white, male, single, aged 48, tailor by occupation, was admitted to the Medical Out-Patient Department of the University of California Hospital, Sept. 15, 1919, complaining of a feeling of pressure in the epigastrium, constipation and belching, especially at night.

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8. Meyer, J.: Polyposis gastrica (Polyadenomata), J. A. M. A. **61**:1960 (Nov. 29) 1913.
9. Hayem: Presse méd. **2**:53, 1897.

Family History.—The patient's father died aged 79 of an unknown cause; the mother died during childbirth; one sister died at birth; one sister is living and well; one brother has stomach trouble. There is no history of cancer or tuberculosis in the family.

Past History.—The patient was born in Germany, emigrated at the age of 17 to the Middle West of the United States; when he was 25, he came to San Francisco, where he has made his home up to the present date. Besides the usual childhood diseases, he thinks he had the influenza about one year ago. There is no history of venereal diseases. In September, 1919, his tonsils were removed. His habits are regular; uses neither tea nor coffee in excess, but before his present illness he was accustomed to drink considerable beer; he has smoked a pipe excessively. During the past year his bowels have been constipated and there has been some nycturia once or twice at night.

Present Illness.—The patient was in good health until March, 1919, when he noted a sensation of fulness in the epigastrium, especially in the left side; the sensation was as if the stomach were full of gas and compelled him to belch frequently. This gas seems to press on the heart and cause palpitation, which is most marked at night. He does not suffer severe abdominal pain, but the fulness and pressure are present often before meals and are relieved at times for an hour after eating. His appetite has remained good. Frequently
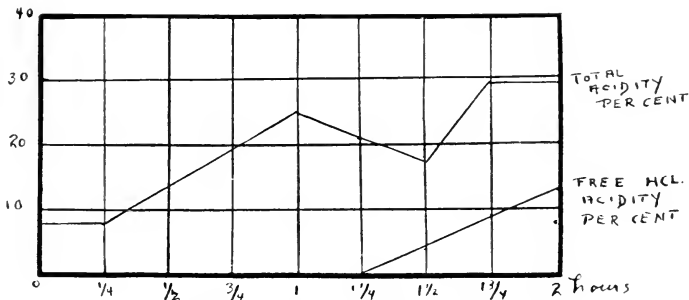
Fig. 1.—Fractional gastric analysis. Ewald test meal.

he has tried to vomit to relieve the distress, but without success. About one month ago he noted that his stools were black and tarry. He also thinks that he has been jaundiced several times since last March and that his constipation has been more marked since his present illness. He has noticed a slight shortness of breath for the past six weeks. There is no evidence of cough or night sweats. In March, 1919, his weight was 165 pounds; he thinks he has lost about 25 pounds since that time.

Physical Examination.—The patient is a fairly well developed and well nourished man of middle age, rather short and of heavy stature. Temperature, 98.2 F.; pulse, 74; respiration, 20. Height, 5 feet, 7 inches; ideal weight, 148 pounds; actual weight, 140 pounds. Blood pressure: systolic, 115; diastolic, 65. His hair shows the normal distribution with beginning baldness over the top of the head. The skin is dry with a moderate amount of pigmentation, particularly over the face. The eyes are normally set, the pupils equal, rather small and react to light and accommodation; the extra-ocular movements are good. The nose and ears on superficial examination are normal. The tongue is moderately coated and protrudes in the midline without tremor. The teeth are stained, probably from tobacco. The tonsils have been removed recently. Neither general nor local glandular enlargement is found. The chest is negative. The heart is within the normal limits as regards size, shape and position; the apex beat is distinct in the fifth left space, 10 cm. from the

midsternal line; the sounds are regular and rather distant; there are no mur-
murs; the pulmonary second sound is equal to the aortic second sound; the
radial pulses are equal and regular. The vessel wall is not felt. The costal
angle is rather wide and there is moderate depression of the epigastrium. The
abdominal walls are lax and soft, and there are no abnormal masses felt and
no visible peristalsis. On rather deep pressure in the epigastrium there is
slight tenderness which is not definitely localized. No tumor mass can be
palpated. There is also slight tenderness to deep palpation in the left lower
quadrant. The extremities are negative and the deep reflexes are equal and
active throughout. Rectal examination shows no hemorrhoids, external or
internal; the sphincter is normal. No perirectal glands are palpable. The
prostate is small and soft and the median fissure is well marked.
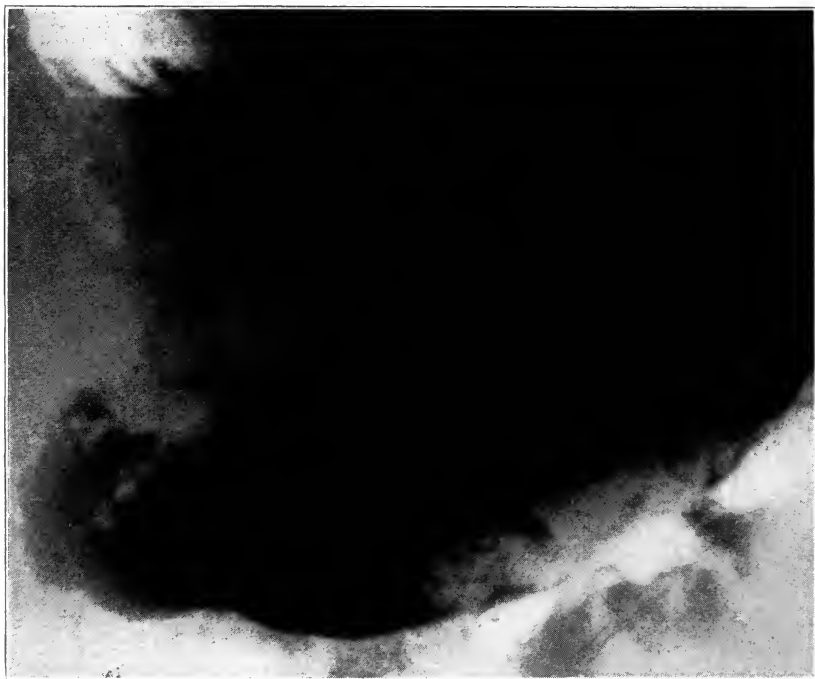
Fig. 2.—Roentgenogram picture showing large, complete filling defect in
the greater curvature after six hours. In the lower portion of this defect
there is only slight mottling, with the finger-print pattern described as the
typical lesion of benign gastric tumors.

Laboratory Findings.—Wassermann blood reaction is negative. Fractional
gastric analysis is shown in Figure 1. Residue from fasting stomach, 150 c.c.
Occult blood test positive (benzidine). Many pus cells and much mucus
present.

Urine examination of single specimen: Specific gravity, 1.020; urine clear,
reaction acid; albumin and sugar negative; sediment negative.

Blood examination: Hemoglobin, 90 per cent. (Sahli); red blood cells,
4,800,000; white blood cells, 8,600. Differential count: polymorphonuclears,
65 per cent.; small mononuclears, 28 per cent.; large mononuclears, 7 per cent.

Stool examination (meat-free diet): Benzidine test positive.

The results of roentgen-ray examination are shown in Figure 2.

Fluoroscopic Examination: Lung fields show a wide aortic arch and a slightly enlarged heart. The diaphragm moves well and equally on the two sides. No delay is noted in the esophagus. The stomach tone is good, it is readily movable and its position is normal. There is no residue after six hours. There is a large defect in the greater curvature. The waves start high up on both curvatures and pass clear through over the lesser curvature, but fade out in the region of the defect in the greater curvature to reappear again below. The pyloric and duodenal caps are normal. The previous meal is found in the terminal ileum, cecum and the transverse colon, all of which are freely movable, separable and not tender.

Diagnosis.—Carcinoma of the stomach—Dr. Ruggles.
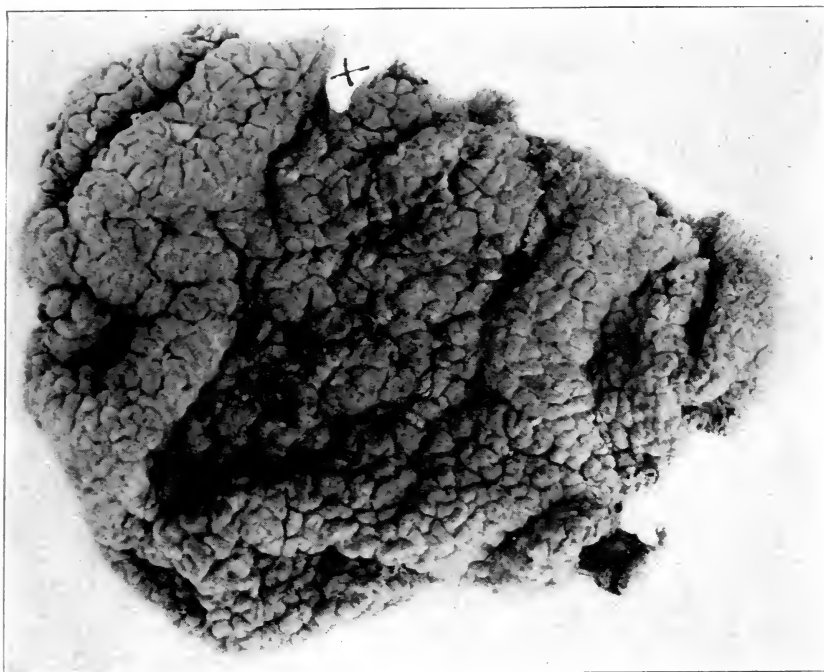
Fig. 3.—Specimen removed at operation.

CLINICAL SUMMARY

A tailor, aged 48, with a history of epigastric pain and belching; family history and past history unimportant, has been ill about eight months, with history of loss of weight. The finding of practically negative physical examination, except for epigastric tenderness, points to the possibility of a stomach condition. The absence of free hydrochloric acid in the stomach juice and the finding of occult blood in the stools together with the fluoroscopic picture, which revealed a large, clean cut defect in the greater curvature, indicated a diagnosis of gastric carcinoma. The patient was then sent to the surgical service of the hospital.

Operation.—Exploratory laparotomy, Dr. Wallace I. Terry, Oct. 29, 1919: A longitudinal incision was made through the right rectus muscle, extending from the costal margin to 3 cm. below the umbilicus. The abdomen was opened in the usual way. The foramen of Winslow was open. The abdominal contents were apparently negative. The stomach externally showed no patho-

logic signs, except that there were a few soft lymph glands near the attachment of the great omentum to the greater curvature of the stomach. At the greater curvature of the stomach, however, a mass could be palpated within, which was readily movable under the finger and not infiltrating the muscular or peritoneal coats. The impression conveyed was that of a large doughy tumor about 8 cm. in diameter. The presence of such a tumor immediately threw doubt on the preoperative clinical diagnosis. A frozen section of one of the glands above mentioned was made and no carcinomatous changes could be demonstrated in this tissue. The stomach was therefore opened to confirm the impression that a polypoid condition of the gastric wall was present; this proved to be correct. After closely applying abdominal tapes to the gastric wall the stomach was opened, and then grasping the periphery of the tumor with a couple of Allis forceps, it was excised. The great omentum had to be detached from this portion of the greater curvature. The wound was sewed together after the manner of Finney with mattress sutures of iodized catgut, running stitch, with a reinforcing stitch over this. So great a portion of the greater curvature and walls of the stomach had been removed, it was feared that an hour-glass stomach would result; consequently, a gastro-enterostomy was also performed. The cardiac end of the stomach was laid next to the proximal loop of the jejunum by means of the Allis forceps, the stomach being brought through the opening in the mesocolon, which had been turned up over it. The stomach was then grasped with an intestinal clamp and the jejunum with a Moynihan clamp. There was some difficulty in approximating the two pieces of bowel on account of the small amount of stomach that could be seized through the rest of the mesocolon. They were, however, finally joined by an approximating stitch of catgut and the two portions of bowel cut longitudinally, and the opposing and remote edges approximated by means of a Connell stitch. A last reinforcing stitch was applied to the now closed stoma and the jejunum fixed to the hole in the mesocolon by means of three stitches of iodized catgut. The abdomen was closed in the usual manner.

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Case of Dr. W. I. Terry, Oct. 31, 1919. H. S., S. 19, 792.

Gross Pathology.—The specimen (Fig. 3) consists of a portion of stomach wall measuring 13 by 10 cm. The peritoneal surface does not show anything grossly abnormal, except some clamp marks and a few hemorrhagic stains. The mucosal surface presents a tumor mass measuring 11 by 10 cm., surrounded by a minimum of what in the gross appears to be quite normal stomach mucosa. The superficial picture shows closely packed papillomatous growths, thrown into folds, which resemble very much in color and contour brain cortex. It is relatively easy to separate the various convolutions (that is, the individual papillomas) clear to their bases. There can be traced a gradual increase from the apparently normal mucosa to the pronounced papillomatous outgrowths. No gross evidence of necrosis can be made out in any of the papillomas, although there is a slight amount of hemorrhagic discoloration in the tips of some of them. On section the gross picture does not show any increase in the muscular or connective tissue elements of the stomach wall proper. There is no gross evidence of any extension downward into the layers beneath the mucosa nor are there any other suggestions of malignant change. The mucosa displays a decided thickening in places as much as 0.5 cm. Gross impression: Papillomatosis of the stomach (benign).

Microscopic Pathology (Figs. 4 and 5).—Duplicate sections of the tumor were stained respectively with the routine hematoxylin and eosin, for muscle and connective tissue with Van Giesen's, for connective tissue by Mallory's method, and for elastic tissue by Weigert's stain. Sections show a picture of stomach mucosa displaying a gradual increase from normal thickness to

tremendous hypertrophy and thickening in a definitely papillomatous arrangement. The general picture of this hypertrophy is that of gastric glands. The tubular glands are greatly elongated, show a marked corkscrew type of growth and many branchings. The mucosal cells are invariably columnar in type and in many places, especially in the depths, show wonderfully clear differentiation from each other; the distinction between the chief and parietal
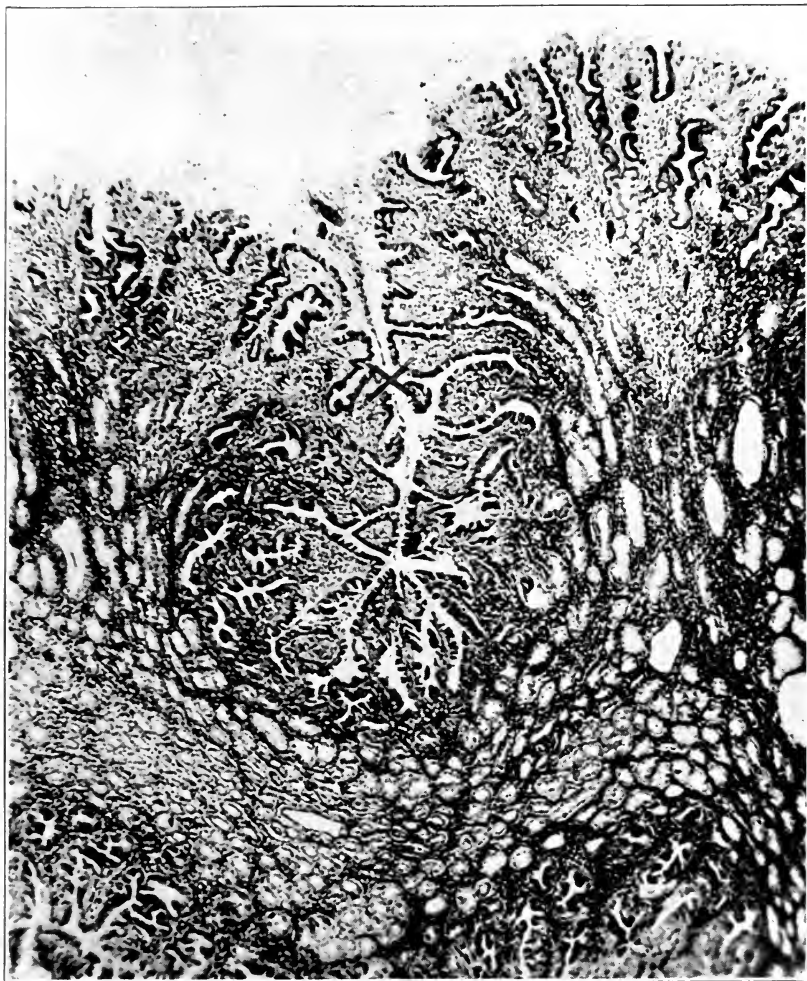
Fig. 4.—Photomicrograph, low power. Block taken from point X on Figure 3.

cells is striking. Occasionally, one sees some atypical nuclei which are definitely shown to be the result of degeneration instead of mitosis. The stroma is minimal in amount. The sections stained to show muscle and connective tissue by Van Giesen's method show the stroma of the papillomatous outgrowths to be connective tissue and to contain no muscle. The connective tissue is verified by Mallory's stain. Weigert's stain brings out no trace of elastic fibers within these structures. These special stains, more especially

the Mallory's, demonstrate the fact that there is no breaking up of the basal membrane of the glandular structures and show it to be everywhere intact. The stroma shows in places some edema, some infiltration with round cells, plasmalike cells, red blood cells and an occasional polymorphonuclear. The stomach musculature proper is everywhere normal in appearance.

Diagnosis: Papillomatosis of the stomach—Granville S. Delamere, M.A.

Clinical Course.—The postoperative course in the hospital was uneventful. November, 1919, a gastro-intestinal series following a bismuth meal showed
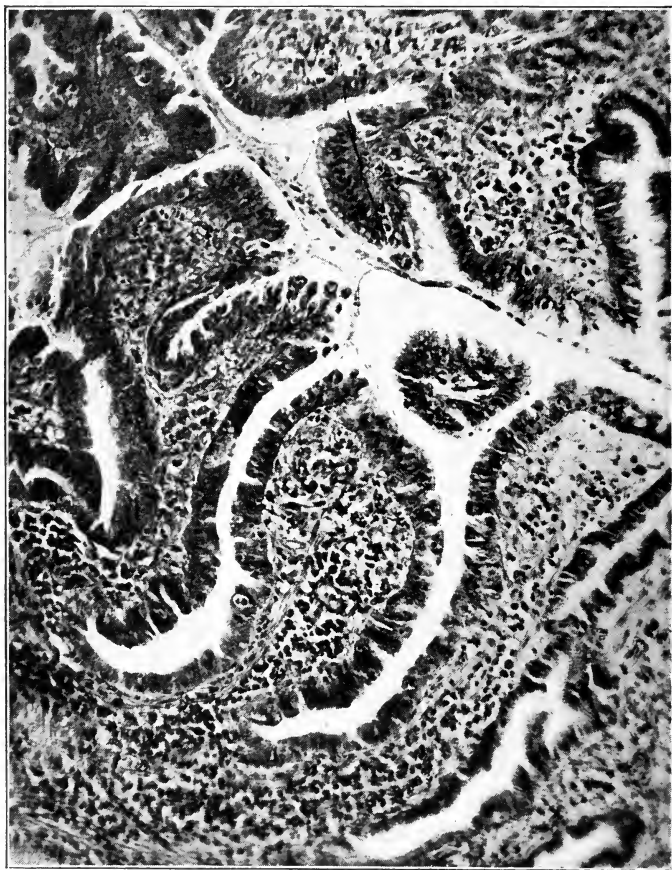
Fig. 5.—Photomicrograph, high power. Field X on Figure 4.

a large postoperative defect in the middle third of the stomach, the pyloric and duodenal caps normal, and the gastro-enterostomy apparently working well. There was some delay in the duodenojejunal juncture with some moderate amount of reversed peristalsis. Conclusion: Postoperative condition.

Nov. 22, 1919, the patient was discharged from the surgical service and advised to report regularly to the Medical Out-Patient Department. Dec. 11, 1919, in the Surgical Out-Patient Department a sigmoidoscopic examination was done (Dr. Hyman). The tube was easily introduced a distance of 23 cm. and by means of distention with gas the bowel wall was visible for 5 cm. farther. The picture was entirely normal.

Feb. 19, 1920, a fluoroscopic examination was made. Gastro-enterostomy was seen to be functioning well; meal also left stomach through the pylorus; postoperative defect seen in the median third of the stomach, but no evidence of obstruction.

March 20, 1920: The patient's course in the Medical Out-Patient Department has been uneventful. Patient has gained twenty pounds in weight and is feeling well.

ETIOLOGY

Nothing definite is known about the cause of gastric polyposis. Its frequent association with other diseases, such as gastritis, hypertensive cardiovascular disease, and syphilis has led to interesting speculations.

SYMPTOMATOLOGY

There is nothing pathognomonic in the symptoms of this condition, although there are, at times, certain suggestive evidences of the disease. The fact that many of the cases are discovered at necropsy, when the existence of ante mortem gastric disease is not suspected, demonstrates its frequent silent nature. Clinical manifestations, however, when present, depend principally on several factors, namely, the size, location and nature of the growth, and particularly its relation to the pyloric region of the stomach. It is found more commonly in men past middle age.

Nonpedunculated, broad based masses on the greater curvature may remain symptomless or more commonly produce vague, indefinite symptoms of an epigastric dragging sensation, followed by a desire to belch and eventually to vomit. The onset of such disturbances does not appear to have any relation to meals, since it is as often present before meals as after or between meals. Meyer, in his careful study, calls particular attention to the type of vomitus which he regards as of great significance. The vomitus he describes contains an excessive amount of mucus of an egg-white appearance and in his case a small benign polyp (adenoma) was recovered, which enabled him to make the pre-operative diagnosis. Further, it is noted in these cases, that there is usually absence or greatly reduced amount of free hydrochloric acid, in other words, an achylia gastrica or hypoacidity.

Pedunculated and less commonly nonpedunculated growths, situated on the stomach wall near the pylorus may prolapse and present the typical clinical picture of pyloric obstruction, partial or complete. Wade [10] reports a case which is a spectacular example of this variety.

Hemorrhage, slow and long unrecognized, is a frequent finding in these cases and is due to the great vascularity of these tumors of the mucous membrane. This accounts for the usual finding of occult blood in the fasting contents of the stomach and in the stools.

10. Wade, H.: Intussusception of the Stomach and Duodenum Due to Gastric Polyposis, Surg., Gynec. & Obstet. **17**:184, 1913.

The appetite is variable; perhaps, more often it remains good and for this reason is in marked contrast to anorexia so prevalent in the cases of gastric malignant disease.

The general nutrition, weight and blood picture are also variable, but, as a rule, they are less altered than in the carcinoma cases, particularly when pyloric obstruction has occurred. Careful observations in regard to these latter conditions are among the most helpful adjuncts in the final estimation of a case.

It may be said, in general, that palpable masses are more common in these cases when the growth is large and located near the pylorus, but it is surprising in how many cases nothing abnormal can be determined by abdominal palpation. Intense pain in the epigastrium is recorded in an occasional case and is in some instances the symptom which first brings the patient to the physician.

The duration of the history in these cases is, at times, significant; the fact that definite symptoms may have been present for a long time without apparent progression and with little or no change in the patient's general health is strong evidence against the presence of malignant disease, and should suggest the possibility of a benign tumor condition.

DIAGNOSIS, WITH SPECIAL REFERENCE TO ROENTGEN RAY

Gastric polyposis, as has been indicated, besides being an accidental finding at necropsy, may also be discovered in the course of surgical procedures. The early accurate roentgenographic description by Carman in Meyer's case of gastric polyposis, in which a fairly characteristic picture of the disease was first outlined, might seem to have indicated that definite roentgenographic manifestations were always to be expected in such cases. Unfortunately, this has not proved to be the case, since we know now that gastric polyposis may present roentgenographic evidence so similar to that found in cases of gastric carcinoma that not even an expert roentgenologist can differentiate the two conditions. The interpretation of the findings in benign polypoid tumors from the presence of gastric carcinoma is the prime difficulty. Many recorded instances exemplify this, and the case reported above is a typical example in which roentgen-ray interpretation was misleading both to the internist and to the roentgenologist, because the manifestations conformed more to the usual picture seen in carcinoma of the stomach than to the rarer condition of gastric polyposis. In the two cases of polyposis reported by Friedenwald and Finney,[11] notwithstanding the roentgen-ray studies, the diagnosis in both instances was gastric carcinoma.

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11. Friedenwald, J., and Finney, J. M. T.: Gastric Polyposis, Am. J. M. Sc. **154**:683 (Nov.) 1917.

It would appear that when the typically mottled, fingerprint, filling defect is present in the stomach in conjunction with other evidence in the history, physical examination and laboratory findings pointing to benign gastric tumor, a diagnosis of gastric polyposis may be justified, but, conversely, it must be remembered that roentgenograms strongly suggesting malignant new growths may prove to be benign tumors.

In view of the foregoing statements, it appears that roentgen-ray studies of the stomach have strengthened the surgeon's position in regard to the advisability of exploratory laparotomy in some of the presumably advanced cases of gastric carcinoma, since in rare instances the finding of a benign tumor may be a surprise to the surgeon and a "new lease of life" to the patient. The roentgen ray affords valuable evidence in some cases and misleading evidence in others. Carman and Miller [12] state that in view of the limited number of these cases our roentgen-ray experience is still necessarily meager, and, therefore, it is not possible to lay down hard and fast rules concerning the roentgen manifestations.

Besides the roentgen-ray studies of the stomach, other helpful methods of investigation should include a careful history, a thorough general physical examination, and numerous laboratory tests. When the combined results of these procedures are evaluated and combined with the roentgen-ray findings, we have at our command the methods which offer the greatest expectation of a correct diagnosis. [13]

SURGERY

Excision of the tumor mass and such reconstructive measures as may seem indicated in the individual case offer the greatest hope for satisfactory results in cases of gastric polyposis.

SUMMARY

A case of gastric polyposis of the papillomatous type is reported in which the clinical and roentgen-ray diagnosis was carcinoma of the stomach. Exploratory laparotomy revealed a broad based benign tumor situated in the greater curvature of the stomach; this tumor was excised and following this the patient has had an uneventful convalescence and six months later has had no recurrence of his former symptoms.

12. Carman, R. D., and Miller, A.: The Roentgen Diagnosis of Diseases of the Alimentary Canal, Philadelphia, W. B. Saunders Company, 1917.

13. For a complete bibliography of the older literature see Friedenwald and Finney (Footnote 11).

CLINICAL AND ELECTROCARDIOGRAPHIC OBSERVATIONS ON INVERSION AND OTHER ANOMALIES OF THE P WAVE *

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Interest regarding the diagnostic and prognostic significance of inversion and other anomalies of the P wave of the human electrocardiogram continues to grow. Much of this interest centers around the problem of interpretation. Likewise, the frequency of this finding seems to increase, although this is probably the result of attention being focused on it. During the past six months, approximately three hundred curves have been taken in the electrocardiographic laboratory of the Michael Reese Hospital, of which fully 20 per cent. have shown inversion of the P wave, usually in Lead III. In view of this frequency, and because exact knowledge regarding its significance is meager, it seemed worth while to analyze the curves showing this phenomenon and summarize the findings thus obtained.

It is generally accepted that the physiologic auricular complex—P — is an upright wave which results from auricular systole and "expresses the origin of the heart beat at the normal site of impulse formation and the passage of the wave through the whole of the auricular tissue in definite directions."[1] According to Hoffman,[2] the P wave accompanies conduction over the auricle. Variations in this wave, therefore, in height, length, direction, configuration, etc., are dependent on deviations from the normal, either at the site of impulse formation (pacemaker) or of the conduction paths through the auricle. Certain factors responsible for these variations have already been described.

Einthoven[3] demonstrated that vagal stimulation may so reduce the height of the P wave that it becomes diphasic. Thomas Lewis[4] showed that a change in the shape of P indicated a change in the location of

1. Lewis, T.: Clinical Electrocardiography, Ed. 2, 1918, London.

2. Hoffman: Die Electrocardiographie, 1914, Weisbaden, Bergman.

3. Einthoven, W.: Weiteres über das Elektrokardiogram, Arch. f. d. ges. Physiol. **122**:540, 1908.

4. Lewis, T.: Galvanometric Curves Yielded by Cardiac Beats Generated in Various Areas of the Auricular Musculature, The Pacemaker of the Heart, Heart, **11**:2, 1910.

the pacemaker. He found, for Lead II, that when the impulse origi-
nated in the upper portion of the auricle, the P wave was upright.
When the impulse originated in the median part of the auricle, P
approached the isoelectric state. When it originated in the lower part
of the auricle, P was inverted.

Ritchie,[5] v. Hoesslin,[6] Einthoven, Fahr and deWaart [7] ascribed the
inversion of P, which they observed after vagal stimulation, to some
change in the pacemaker, or to some change in the path of contraction
wave over the auricle.

Hering [8] showed that in the first lead, the size and direction of P
may not be affected markedly, even when the impulse originated in
the A-V node.

Goddard [9] believed that inversion of P occurred in Lead III only,
that it occurs at all ages, and that the size and shape of P may vary in
the same curve, that an inverted P in one record may appear upright in
a later tracing, and vice versa.

Wilson [10] reported three cases showing changes in the location of
the pacemaker associated with deep respiration, and believed that the
changes might be divided, first into migration of the pacemaker within
the sino-auricular node or its immediate neighborhood, and second,
migration of the pacemaker from the sino-auricular to the A-V node.

Carter and Wedd [11] summarized their findings as follows: "We
believe we may divide our series of inverted P waves seen in Lead III
into two distinct groups. One in which there may be a variation of
the site of the pacemaker in its relation to Lead III, conspicuously
under the influence of the vagi and digitalis. Second, in which the
relation of the pacemaker to Lead III is such that a constantly nega-
tive P 3 is present, utterly uninfluenced by atropin, vagal pressure of

5. Ritchie, W. F.: Action of the Vagus on the Human Heart, Quart. J.
Med. **6**:47, 1912.

6. v. Hoesslin, H.: Beobachtungen über den Einfluss der Vagus auf dass
Menschlichen Herz, Deutsch. Arch. f. klin. Med. **113**:537, 1914.

7. Einthoven, Fahr and deWaart: Ueber die Richtung und dier manifeste
Groesse der Potential Schwankungen im menschlichen Herzen und über den
Einfluss der Herzlage auf die Form des Electrokardiograms, Arch. f. d. ges.
Physiol. **100**:275, 1913.

8. Hering, H.: Rythmische vorhofstach systolie und Pulsus irregularis
perpetuem, München. med. Wchnschr. **111**:2057, 1914.

9. Goddard, C. H.: Changes in the P Wave of the Human Electrocardio-
gram, Arch. Int. Med. **16**:633 (Nov.) 1915.

10. Wilson, F. N.: Three Cases Showing Changes in the Location of the
Cardiac Pacemaker Associated with Respiration, Arch. Int. Med. **16**:86 (July)
1915.

11. Carter and Wedd: Observations on the Occurrence of Inverted and
Diphasic P Waves in Lead III of the Human Electrocardiogram, Arch. Int.
Med. **23**:1 (Jan.) 1919.
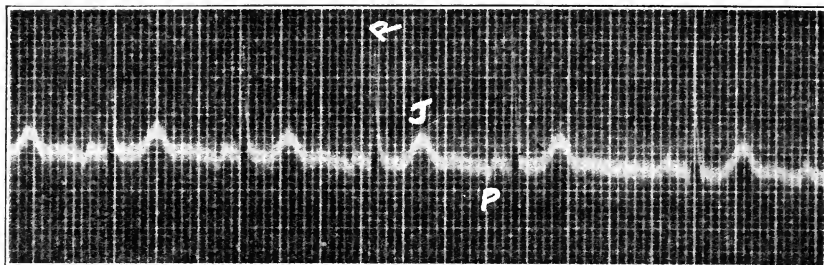
Figure 1
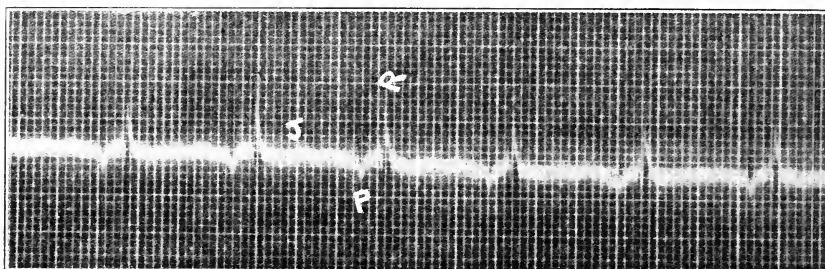
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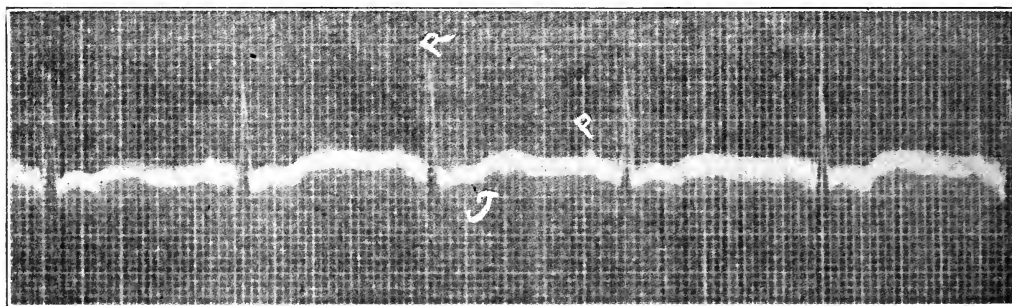
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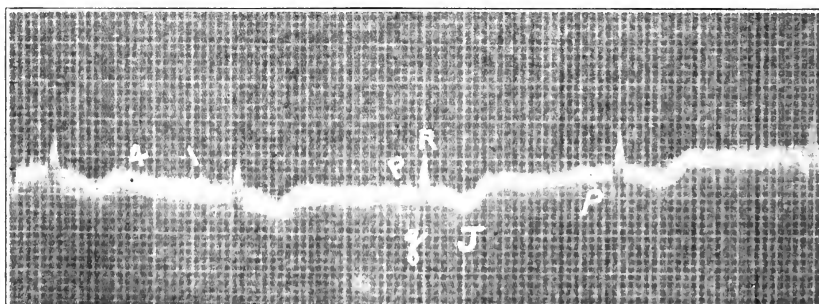
Figure 4

digitalis, due probably to a change in the muscle balance altering the relation of the pacemaker to the axis, or to the distribution of the vagal fibers."

White reported one case showing migration of the pacemaker within the sino-auricular node.

Present knowledge regarding variations of the P wave, therefore, may be summarized as follows:

1. Vagal stimulation (vagus pressure) reduces the height of the P wave, makes it diphasic and causes inversion.

2. The P wave becomes isoelectric when the impulse originates in the median portion of the auricle; inverted when it originates in the lower part of the auricle.

3. Deep respiration causes changes in the appearance of an upright P, flatting and inversion with forced expiration, with a return to upright upon inspiration.

4. Digitalis may cause inversion of P.

5. Atropin may cause an inverted P to become upright.

6. Persistently inverted P waves may occur, uninfluenced by vagus pressure, digitalis or atropin.

7. Inversion of P is usually associated with a decrease in the P-R interval, sometimes with slowing of rhythm, or the setting up of A-V rhythm.

8. Inversion of P is believed to express migration of the pacemaker of the heart from its normal position in the sino-auricular node to some ectopic point lower down in the auricle, even to the auriculoventricular node.

The following cases comprise the ones on which this report is based. For the sake of brevity only the salient points in connection with these cases are given.

REPORT OF CASES

CASE 1.—M. S., aged 12 years. Clinical diagnosis: Sinus arrhythmia. Lead II: Wave at first inverted (P-R interval 0.12); later becomes upright (P-R 0.14), with slowing of pulse (Fig. 1). Lead III: Permanently inverted (P-R 0.12) (Fig. 2).

CASE 2.—S. W. S., aged 55 years. Clinical diagnosis: Pyonephrosis. Lead III: Recumbent posture; P wave upright (P-R 0.16) T inverted (Fig. 3). Lead III: Upright position; P wave inverted (P-R 0.12). T inverted (Fig. 4).

CASE 3.—A. W., aged 60 years. Clinical diagnosis: Fibrous myocarditis. Lead II: P irregularly inverted; auricular and ventricular extrasystoles (Fig. 5). Lead III: P inverted at first (P-R 0.16); later upright (P-R 0.20) (Fig. 6).

CASE 4.—M. M. H., aged 58 years. Clinical diagnosis: Fibrous myocarditis. Lead I: P inconstant and diphasic (P-R 0.16) (Fig. 7). Lead III: P bifurcate (P-R 0.20) (Fig. 8).
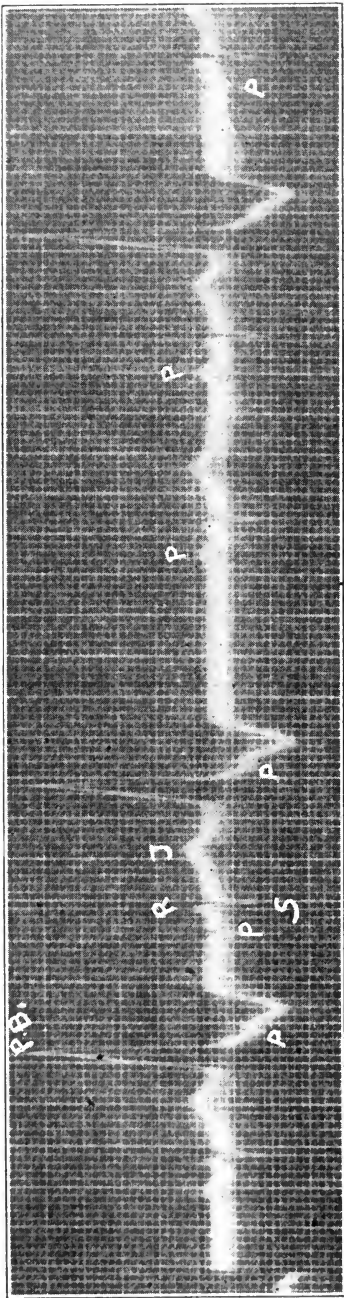
Figure 5
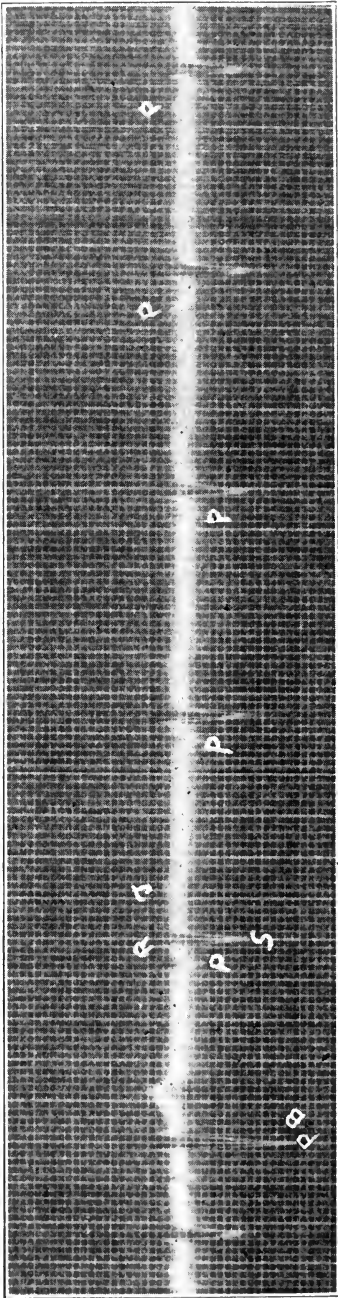
Figure 6

CASE 5.—B. B., aged 11 years. Clinical diagnosis: Subacute myocarditis. Lead III: P diphasic; notching of P-R interval (P-R 0.12) (Fig. 9).

CASE 6.—Miss M. L., aged 40 years. Clinical diagnosis: Fibrous myocarditis. Lead III: P inverted and wide (P-R 0.16) (Fig. 10).

CASE 7.—Miss G. Clinical diagnosis: Postscarlatina and diphtheria; myocardial insufficiency. Lead III: P inverted with exception of a single upright wave. Inverted P bifurcated and wide; later upright and narrow. Inverted P (P-R 0.16); upright P (P-R 0.16) (Fig. 11).

CASE 8.—Mrs. C. Clinical diagnosis: Postinfluenzal myocardial insufficiency. Lead III: P inverted, narrow and shallow (P-R 0.16) (Fig. 12).

CASE 9.— Dr. H. Clinical diagnosis: Myocardial weakness. Lead III: P inverted, varying depths. Muscular tremors (P-R 0.16) (Fig. 13).

CASE 10.—Mr. B., aged 52 years. Clinical diagnosis: Hypertension. Lead III: Diphasic P (P-R 0.16) (Fig. 14).

CASE 11.—Mr. B. F., aged 53 years. Clinical diagnosis: Fibrous myocarditis, myocardial insufficiency, angina pectoris. Lead III: P diphasic bifurcated (P-R 0.16) (Fig. 15).

CASE 12.—Miss W. A., aged 40 years. Clinical diagnosis: Postinfectious myocardial weakness. Lead III: P diphasic (P-R 0.16) (Fig. 16).

CASE 13.—Mr. G., aged 50 years. Clinical diagnosis: Visceral syphilis; Wassermann + + +. Lead III: P upright and wide (P-R 0.18); auricular extrasystoles (Fig. 17). Lead III: After 1/60 grain atropin, P inverted and narrow (P-R 0.11), auricular extrasystoles (Fig. 18).

CASE 14.— Mr. D. Y., aged 56 years. Clinical diagnosis: Myocarditis. Lead III: P inverted (P-R 0.16).

CASE 15.—Miss N., aged 26 years. Clinical diagnosis: Myocarditis, postinfluenzal. Lead III: P inverted (P-R 0.14); auricular extrasystoles.

CASE 16. — Dr. B., aged 34 years. Clinical diagnosis: Myocarditis, postinfluenzal, auricular extrasystoles, dropped beats. Leads II and III: P inverted (P-R 0.32 to 0.36).

CASE 17.—Mr. C. W., aged 35 years. Clinical diagnosis: Myocarditis, postinfluenzal. Leads II and III: P inverted (P-R 0.12); ventricular extrasystoles.

CASE 18. — Mr. R., aged 30 years. Clinical diagnosis: Myocarditis, postinfluenzal, auricular extrasystoles, pulsus bigeminus. Leads I, II and III: Inverted P.

An analysis of these cases brings out the following facts.

All ages are represented, the youngest patient was 11 years, the oldest 60. Clinically, in a majority of instances, some evidence of myocardial insufficiency could be demonstrated, in degrees varying from slight heart muscle involvement to grave forms of cardiac embarrassment. Many are acute or subacute and transitory, or postinfectious (influenzal) (Streptococcus) disappearing within a varying length of time after the etiologic infection has subsided. In six cases in which definite myocardial involvement could be diagnosed, inversion of P was associated with arrhythmia, auricular (occasionally ventricular) extrasystoles. Several cases were found in neurotic (vagotonic?) individuals, following slight acute respiratory infections, excessive smoking, prolonged nervous or mental strain, chronic gallbladder or kidney infections. Two cases were associated with disturbances of respiration, "difficulty in taking a deep breath," and with
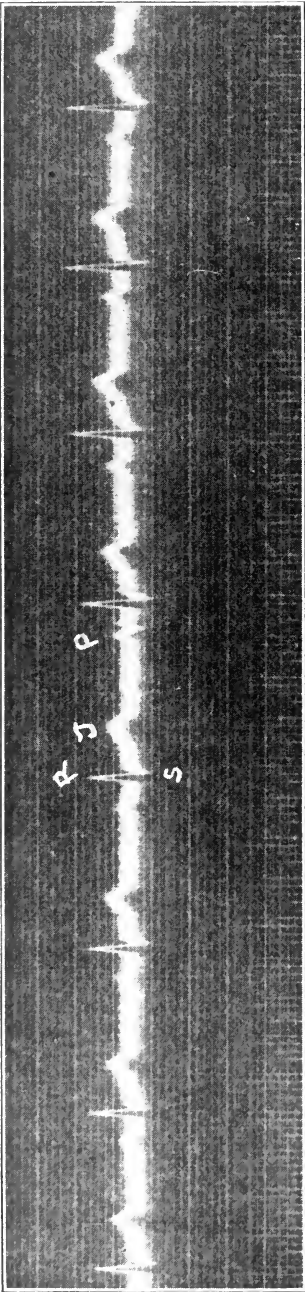
Figure 7
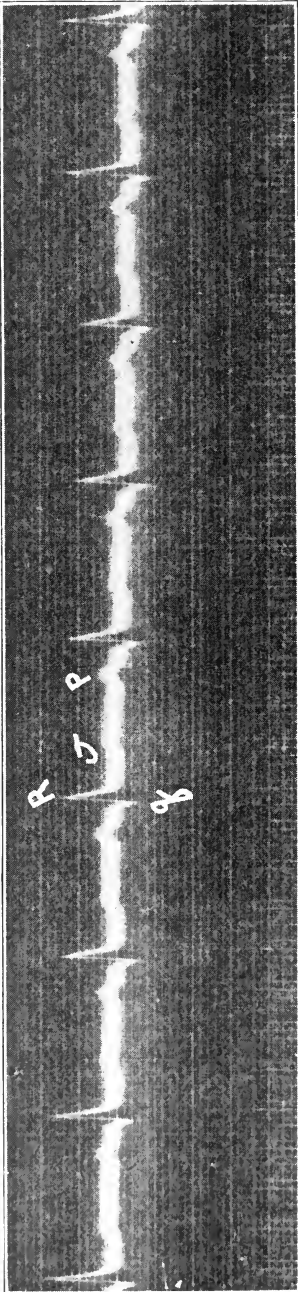
Figure 8
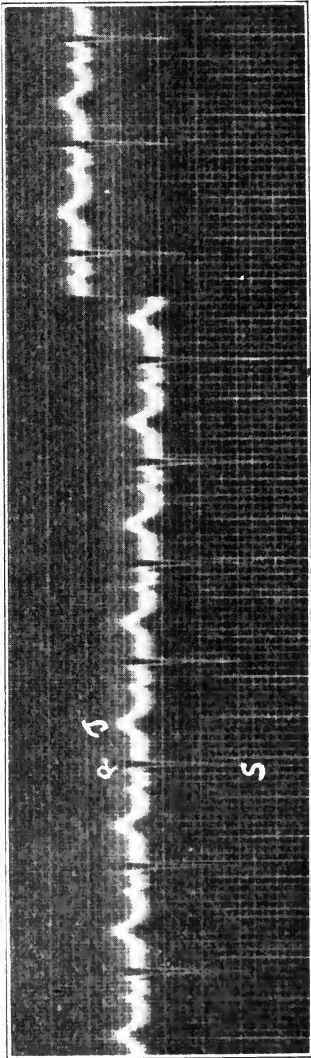
Figure 9

tachycardia on exercise. Three cases of inversion become upright after atropin; one upright P (Case 13) became inverted after atropin. In one case (Case 2) an upright P with patient recumbent, became inverted when patient sat up. In the majority of cases, inversion was present in the third lead only; in five cases it was present in Leads II and III; in one case it was present in all three leads.

Four cases showed regular or irregular alteration of inverted and upright P; in these cases, P-R of the inverted waves was shorter (average 0.04) than that of the upright waves. Width and depth of the inverted waves often was different from the upright waves; at times being narrow and shallow, and at other times being wide and deep. Five cases showed diphasic waves; four showed notched or bifurcated waves.
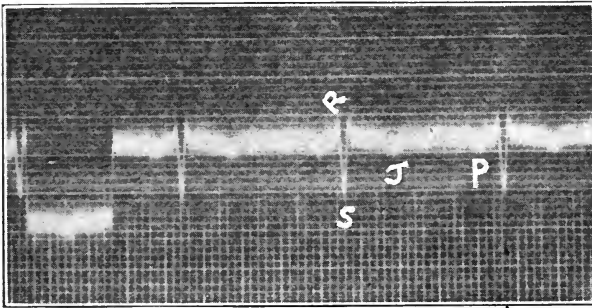
Figure 10

DISCUSSION

Assuming that the various anomalies in the P summit cited above are evidence of a migration of the site of impulse formation (pacemaker) and a consequent disturbance in the passage of the conduction wave through the auricle, one must conclude that such variation is very frequent (20 per cent.), extremely bizarre, and dependent on a number of factors, difficult to correlate. The frequency of inversion in Lead III, and the infrequency in other leads, suggests, as in inversion of T, that this may be a phenomenon of little significance. Against this view is the fact that in a majority of the cases some degree of myocardial weakness could be demonstrated clinically, as well as the fact that most of the patients suffered, or had suffered with acute or chronic infectious processes, factors of etiologic importance in cardiac pathology. Cases in this series in which inversion is associated with auricular extrasystoles gave unquestioned evidence of grave myocardial involvement, so that one may feel justified in stating, that migration of the pacemaker *with* auricular premature contractions is, in the majority of instances, to be interpreted as electrocardiograph evidence
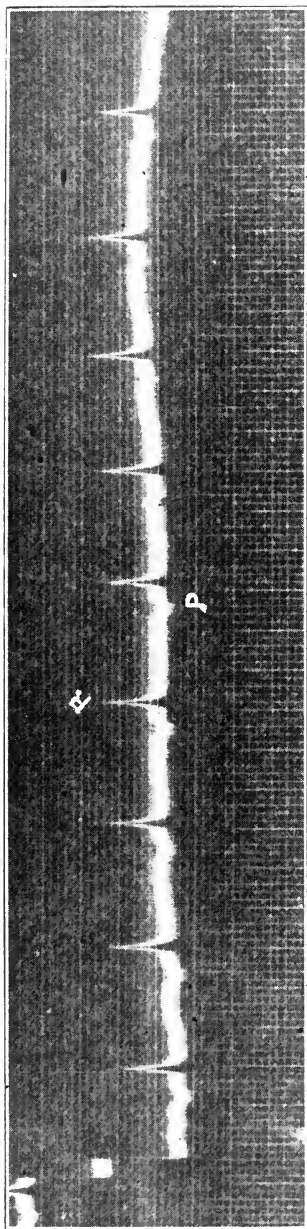
Figure 11
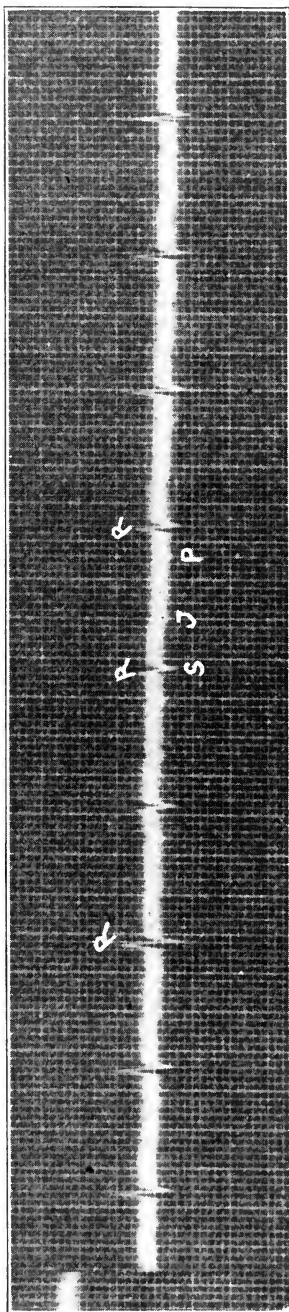
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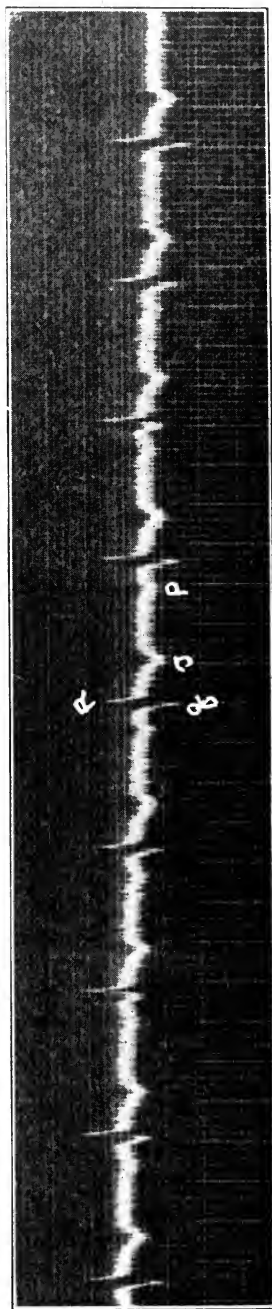
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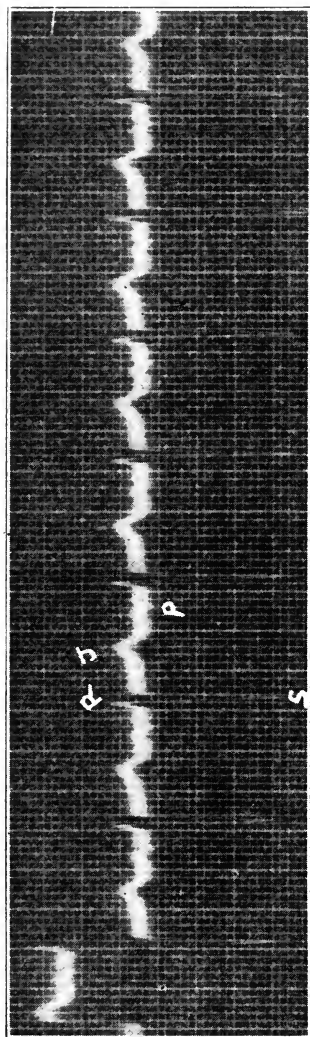
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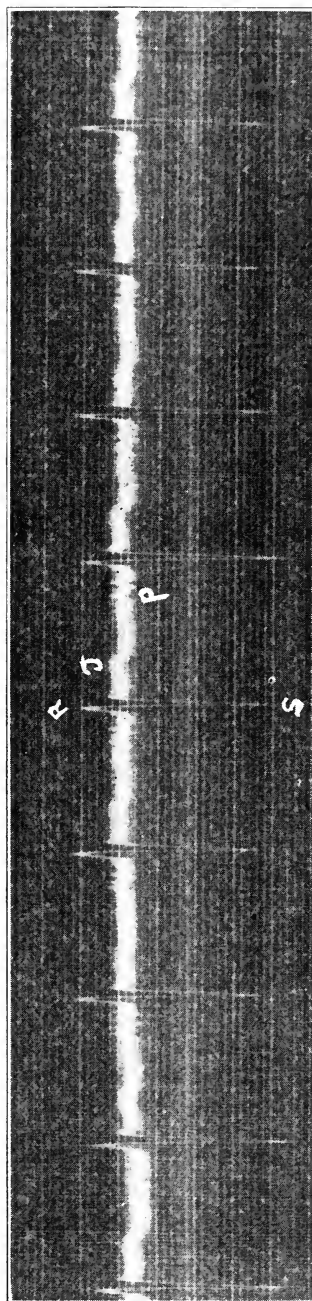
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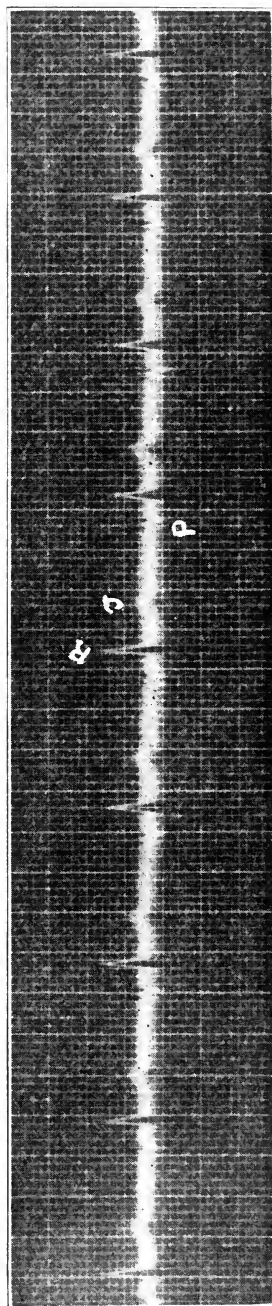
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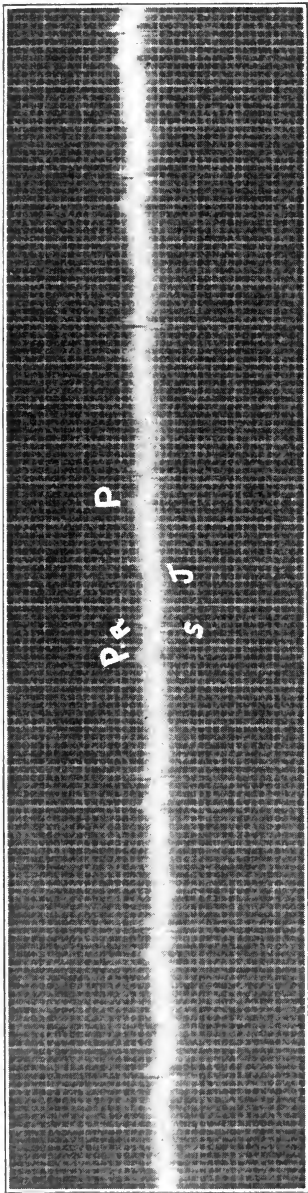
Figure 17
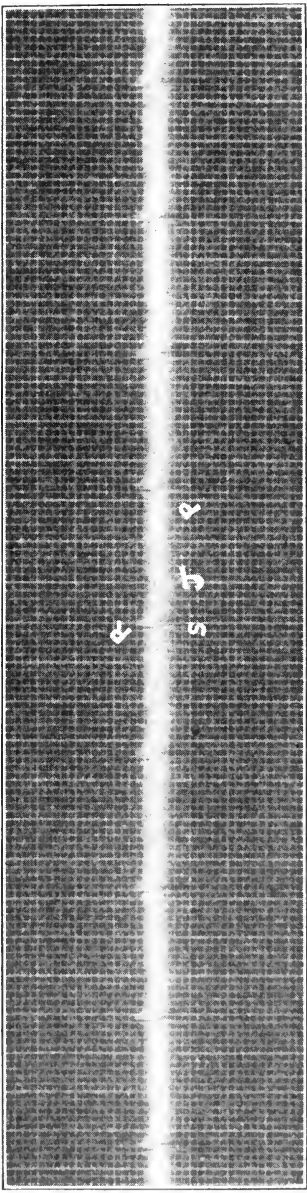
Figure 18

of auricular pathology. In this series, corroborative evidence for this view may be found in such findings as an associated rise of temperature, severe acute angina, pulsus bigeminus, etc. Migration of the pacemaker, however, *without* extrasystoles, especially when found in neurotic individuals, in the presence of prolonged nervous and mental strain, following excessive smoking, associated with disturbance of respiration, relieved (or caused?) by atropin, occurring on assuming the upright posture, is probably to be interpreted as due largely, if not entirely, to variations in vagus control.

SUMMARY

1. Eighteen cases of inversion of the P wave (migration of the pacemaker) are reported; twelve cases with normal rhythm, six cases with arrhythmia (auricular extrasystoles).

2. Inversion of P wave is most frequent in Lead III; five cases showed inversion in Leads II and III; one case in Leads I, II and III; five cases showed a diphasic P; four cases showed a bifurcated P.

3. Analysis of these cases shows that the majority of the patients suffer with varying degrees of myocardial insufficiency and have associated acute or chronic infectious processes. In addition, evidence of vagal influence is frequent, as shown by disturbances in respiration, effect of atropin, occurrence in vagotonic persons, etc.

4. Inversion of P wave *with* auricular extra systoles should probably be interpreted as evidence of auricular pathology; *without* extra systoles, is probably due to variations in vagus control.

5. Electrocardiographic study of cases showing inverted P, or of cases occurring in suspect vagotonic individuals should include the effect of (a) deep breathing, (b) change of posture, (c) atropin and (d) the effort test.

AN ELECTROCARDIOGRAPHIC SIGN OF CORONARY ARTERY OBSTRUCTION

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The study of the form of the electrocardiogram continues to uphold the idea that when the muscular tissue of the heart is diseased, there will follow abnormal variations in the electrical currents due to the heart's contraction. It is hoped to show that obstruction of a branch of coronary artery is followed by a sign which is characteristic of this condition and is readily recognizable in the human electrocardiogram.

REPORT OF CASE

A patient was admitted to the second medical division of the New York Hospital, on the service of Dr. William R. Williams, to whom I am indebted for the privilege of publishing this case. Two hours before admission he had had an attack which was typical of the symptom complex due to an obstruction of one of the branches of a coronary artery.

He was 38 years of age. He had never had rheumatic fever or more than very occasional slight attacks of tonsillitis. Syphilitic infection was denied, though he had gonorrhea at the age of 16, followed by inguinal adenitis. Otherwise he had always been in the best of health until August, 1916, when he had a slight attack of "indigestion," with epigastric distress and eructations of gas. At this time his physician told him that he had heart trouble, although he had never had reason to suspect this himself. About December, 1916, he began to notice that his "wind" was not so good as it had been, and during February, 1917, this trouble became distinctly worse and he also noticed occasional slight aching precordial pain.

March 4, 1917, suddenly, while he was in bed, asleep, he felt a sharp stabbing pain beneath the sternum. This radiated about the left chest and down the left arm and was very severe. He felt very weak and prostrated and thought he was going to die. His heart was beating very heavily, he said, and very slowly. He was not short of breath and did not lose consciousness. After twenty or thirty minutes he vomited, and this was repeated several times during the course of the day. The pain continued severe, although less so after the vomiting.

On admission to the hospital two hours later the heart rate was 44 per minute and the rhythm was noted to be regular, though this seems doubtful in view of later findings. The apex beat was noted as of fair force, the heart sounds of poor quality. The patient appeared cyanotic and showed slightly increased respirations. He complained of precordial pain but not of dyspnea. An electrocardiogram (Fig. 1) was taken by Dr. H. J. Spencer about four hours after the initial attack. At this time his condition was practically as described on admission, and throughout the day he complained of dull precordial pain, made worse by effort, showing slightly increased respirations, but not feeling short of breath, except when lying flat in bed.

During the next two days the cyanosis, increased breathing and precordial pain gradually decreased. His temperature varied from 100 to 101 F. for three days and thereafter was normal. The heart rate varied from 60 to 80 per minute and continually showed the irregularity of auricular fibrillation. The blood pressure was estimated on several occasions and averaged about 130 mm. systolic and 80 mm. diastolic. A Wassermann test was negative.

March 7, when the next electrocardiogram (Fig 2 A) was taken, he was quite comfortable when at rest and appeared to be a practically normal man, although no exertion could be undertaken without marked palpitation and dyspnea and some precordial pain. March 10 he was allowed up in a chair, but felt so weak and was so troubled by palpitation and pain that he did not try it again. While in bed he was quite comfortable and without complaint. Figure 2 B is the record taken March 13, and Figure 2 C was taken March 20. He was up in a chair again March 16, and this time did not complain. His strength improved quite rapidly after this, so that he returned home March 23 after having been walking about the ward without symptoms of distress for the last three days.

He returned to his work as a chauffeur about April 1, and was under my observation until July 11, 1917. During this time he continued to drive his car and often drove very fast. He was also able to change tires without difficulty. It was necessary for him to take digitalis at times to ward off dyspnea on exertion which made its appearance when he stopped the drug. In June, he had another attack, which was possibly a coronary occlusion, though of a smaller artery. While lying in bed, there was a sudden sense of constriction in the chest. He became pale and had to struggle for breath. This passed off after ten or fifteen minutes, leaving him quite weak, but next morning he was all right again and able to go to work. An electrocardiogram taken five days later, was not different from those taken previous to this attack.

The clinical records subsequent to July 11, 1917 are very unsatisfactory. It appears, however, that he continued to come to the clinic at from two to four months intervals. He continued at work for most of the time though there were periods when he was prevented by dyspnea, which was noted as improved after taking digitalis for a time. His disability during the good periods did not keep him from work, and, in fact, in June, 1919, he suddenly fell dead with an attack of severe precordial pain, just after having returned from a day of driving his automobile.

DISCUSSION OF ELECTROCARDIOGRAMS

The record shown in Figure 1, taken about four hours after the beginning of the attack, has very remarkable ventricular waves. Besides the small wavelets marked f f f, due to fibrillation of the auricles, there are the large mounds in Leads II and III, which must correspond to those waves in Lead I which are marked R and T, and which bear a closer resemblance to the usual ventricular waves. It can also be seen that the large waves of Leads II and III are composed of an initial, quickly varying, sharp pointed group, followed by a slower variation, as in the normal ventricular complex. In Lead II, and more especially in Lead III, the slow variation, T, starts from a point well up on the descent of the R wave instead of, as is usually the case, from the base line after the R wave is completed. In Lead III the point of origin of the T wave is almost at the apex of R. These waves then may be divided into a Q R S group and a T wave to bring them in line with the nomenclature of the normal electrocardiogram, and to suggest that the physiologic processes which cause these waves are not essentially different from those causing the analogous parts of the normal electrocardiogram. There is evidently a Q wave in Leads
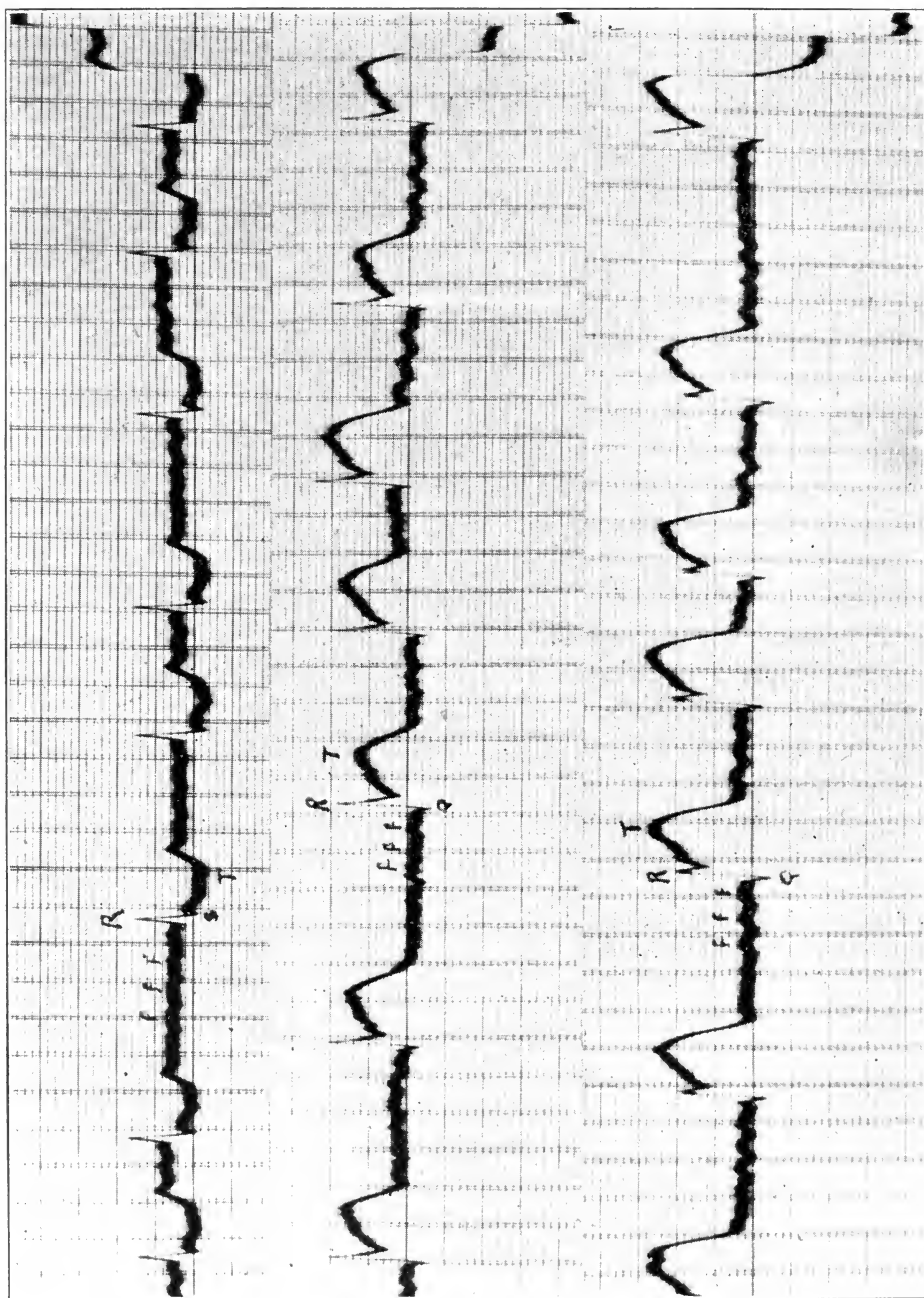
Fig. 1.—Electrocardiogram of patient, taken March 4, four hours after obstruction of coronary artery. The Leads are I, II and III from above downward. The two steps at the end of the lead are caused by introduction of 2 millivolts in the circuit with the patient, and serve as control of the standardization. The space between the corresponding line of each pair of ordinates is 0.20 second.

II and III, and an S wave in Lead I with the T starting from near its peak, as it does from near the peak of the R waves of the other leads.

The Q R S group of this record is not especially remarkable for as far as it developed, i. e., up to the point of origin of the T wave. It suggests that neither ventricle is predominantly hypertrophied. At the point of origin of the T wave there has elapsed from the beginning of this group, only 0.06 second instead of the usual 0.08 second; so it
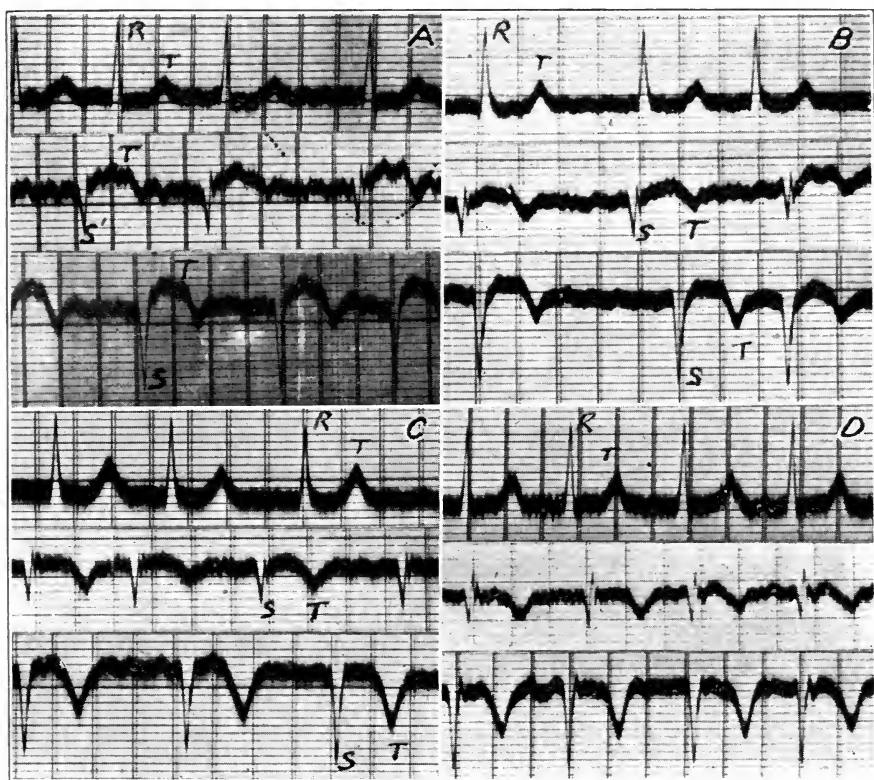
Fig. 2.—Electrocardiograms of same patient taken at later dates. A, March 7; B, March 13; C, March 20; D, May 25. The leads in each group are I, II and III from above downward.

may be said that the Q R S group was not yet completed, was, in fact, interrupted by this very unusual T wave. Whereas the T wave does not usually start until, perhaps, 0.08 second after the end of the Q R S group, and seldom reaches a height of over 5 mm., in this record the T interrupts the Q R S before its completion, lasts for almost 0.40 second and develops a height of 12 mm. in the highest lead.

EXPERIMENTAL PROOF

Such a form for the ventricular waves of an electrocardiogram is most unique and has been noticed in only two other series of curves which have been published. Eppinger and Rothberger injected silver nitrate solution into the deep layers of the left ventricular muscle of a dog and obtained by a lead from the anus and esophagus, curves which bear a very close resemblance to Lead II of Figure 1. Other curves were obtained a few minutes later very much like Lead III. These are shown in Figure 3 A. The anus-esophagus lead does not bear a very different relation to the dog's heart from the relation which Lead II bears to the human heart, so that these curves are as
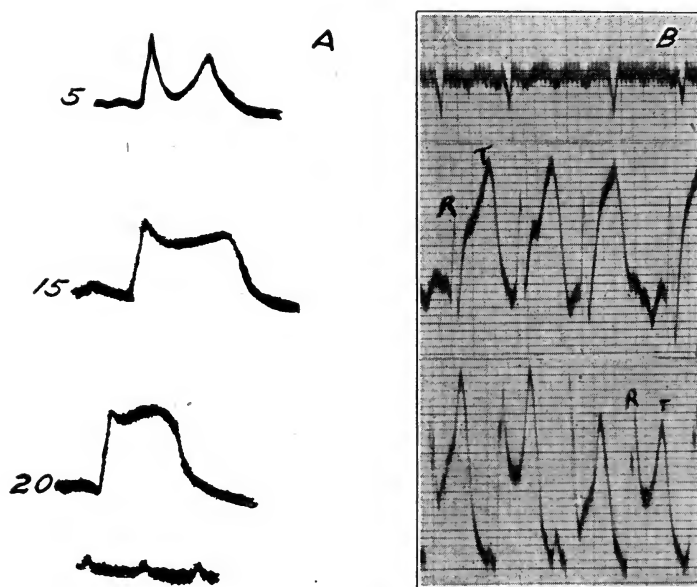
Fig. 3.—A, copy of records obtained by Eppinger and Rothberger after injection of silver nitrate into basal ventricular muscle of a dog. From above downward these curves were obtained five, fifteen and twenty minutes after the injection. 3 B, record obtained by Smith five minutes after ligation of a branch of a coronary artery of a dog. From above downward are Leads I, II and III.

comparable to ours as curves from the lower animals ever can be. They obtained curves of this sort in thirteen out of the twenty-five experiments on the left ventricle, and noticed that the first change was an increase in the height of the T wave, later records showing the origin of the T wave from an increasingly high point on the descent of the R wave, so that eventually it came off from the very peak and extended above it as in Lead III of our case.[1] For this reason it is

1. Eppinger and Rothberger: Zur Analyse des Elektrokardiogramms, Wien. klin. Wchnschr. **22**:1091 1909.

believed that this record of our case indicates coronary artery obstruction, such an obstruction of necessity being followed, as would silver nitrate injection, by an area of muscle degeneration.

More recently a curve has been published by Smith,[2] which was obtained five minutes after ligation of the ramus circumflex sinister of the heart of a dog, and which shows in Lead III the T wave coming off of the descending limb of R about half way down to the base line This curve is reproduced in Figure 3 B. Smith found that the height of the T wave was always increased immediately after the ligation of branches of the left coronary artery, and that its "height seemed to vary directly with the size of the branch ligated." The findings of Smith are in agreement with those of Eppinger and Rothberger, and strengthen the diagnosis in our case.

Injury to the musculature of the right ventricle was found by Eppinger and Rothberger[1] to cause an increase in the size of the T wave also, but the Q R S group was synchronously affected so that the result was a complex resembling that obtained by this lead after injury to the right branch of the A-V bundle in the dog, with abnormally wide Q R S group, small R, large S and large, upwardly directed, T wave. The one record after ligation of the right coronary artery which is published by Smith,[2] shows this same general type of ventricular complex.

THEORETICAL PROOF

All of these experimental facts point to the fact that our case has a large lesion in the left ventricle due to occlusion of a coronary artery, and this conclusion is upheld by two varieties of theoretical evidence from the record itself. First, the Q R S group starts as in a normal electrocardiogram with the ventricular predominance within normal limits. The departure from the normal curve comes at the peak of the S wave in Lead I, at the thickening of the descending limb of R in Lead II and in Lead III at the notching of the R wave. These curves were enlarged photographically and measured, and it was found that all of these points follow the beginning of the Q R S group by from 0.05 to 0.06 second. Lewis[3] has shown that by the time that 0.05 second has elapsed all of the muscle of the heart has entered into contraction, except that portion at the basal part of the left ventricle.

To return to our case: we note that the curve is a normal one until the time when the basal ventricular musculature becomes involved in the contraction. The second bit of evidence from the records is that

2. Smith, F. M.: The Ligation of Coronary Arteries with Electrocardiographic Study, Arch. Int. Med. **22**:8 (July) 1918.

3. Lewis: The Spread of the Excitatory Process in the Vertebrate Heart, Phil. Tr. Roy. Soc. London, Series B, **207**:221.

the T wave of this record is downward in Lead I and upward in
Leads II and III, so that during this period, when all of the ventricular
muscle is contracting and when in normal hearts there is practically
no flow of current, we find a very large current in this patient, the
predominant direction of which within the heart is toward the right
as opposed to the left half of the heart, toward the apical as opposed
to the basal half, and toward the lower as opposed to the upper half.[4]
In Figure 4, the shaded area, projected right through the substance
of the ventricles, is the only region of the heart which could produce
a current fulfilling these qualifications if by reason of a much increased
activity its action current should become predominant over all other
currents at this time.   This is thought to be the mode of production
of the T wave of Figure 1, for the area affected by an arterial occlu-
sion would become an area of anemic necrosis, and the first physiologic
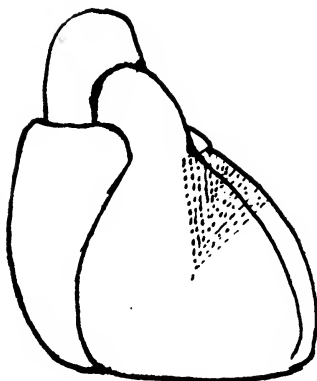
Fig. 4.—Diagram of heart showing probable region of the ventricles affected
in the patient of Figures 1 and 2.

action of this would probably be a brief increase in the chemical
activity of the area, although very shortly the area would cease to
function. This hypothesis is supported by the findings of Eppinger
and Rothberger.   They found, as has been said, that silver nitrate,
injected into the basal part of the left ventricle, gave a high T wave
by the anus-esophagus lead, i. e., produced a predominance of current
within the heart in a direction from base toward apex, but they also
found that cooling of this same region by the ethyl chlorid spray gave
a downwardly direct T wave,[1] i. e., a current flowing in a direction
from apex to base within the heart.   Cooling with ethyl chlorid would
certainly lead to a diminution of the chemical processes of contraction
in the area affected, and the silver nitrate had quite evidently the

4. See in this connection Einthoven, W.: Weiteres über das Elektrokardio-
gram, Arch. f. d. ges. Physiol. **122**:576, 1908.

opposite effect. Eppinger and Rothberger did not take records of their dogs for more than a few hours, but Smith's later records, as well as those of the case here reported, show that the T wave eventually assumes an opposite direction to that which it takes at first. The brief increase in the chemical activity is followed by a diminution.

<center>LATER RECORDS</center>

The next record of this case was taken March 7, three days after the attack. This is shown in Figure 2 A, and bears a closer resemblance to the usual electrocardiogram. The Q R S group shows the absence of R in Lead III, and the deep S in that lead which results from predominance of the mass of the left ventricle. This group does not show an abnormal duration, so that we may say there is no prolongation of the time taken for the spread of the contraction throughout the ventricular muscle,[3] although the notching of the upward limb of the S wave in Lead II, taken together with the broadening of this upward stroke in Lead III, indicates that there is some abnormality in the spread of the contraction wave. The T wave has changed considerably, so that in Lead I it no longer has a downward but an upward direction. In Leads II and III the former upward direction is retained but the amplitude is much smaller, and at the end of this wave at the same time interval after the Q R S group as in the peak of the upward T wave in Lead I, there appears a small downward wave in Lead III. A record taken March 13 is shown in Figure 2 B and is practically the same as that shown in Figure 2 A, except that the rate has been slowed by digitalis, and that there is a definitely downward T wave in Lead III while one is apparently developing in Lead II, as it did in Lead III, by the latter part of this deflection dipping below the line, the part immediately after the Q R S group remaining as an upward deflection. Lead III still continues to show a slight upward deflection during this period.[5]

The next record was taken March 20, and is shown in Figure 2 C. The Q R S group is unchanged from the last record, and the downward T wave is well developed in Lead II and of large size in Leads I and III, especially the latter, where it shows its maximum value. In none of the leads does the interval between Q R S and T depart far from the base line of the record, though it does so in Leads II and III. After

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5. This distinction, between the direction of the peak of T and that of the current before this peak, has been neglected by most writers. It should not be neglected for the current between S and T has frequently a direction different from that of the T wave itself, and of course is indicative of the muscular activity of the heart at an earlier part of the heart cycle than the peak of T. It may vary when the T wave does not, a common observation after the administration of digitalis being that this interval will be changed at a much earlier stage of the digitalis effect than the T wave itself.

this date the electrocardiogram changed very little for as long as it was observed, which was until July 11. Records taken March 19 and April 6 showed ventricular waves practically identical with those of Figure 2 C. Figure 2 D is the record taken May 25, and shows a slight change in Lead II in the Q R S group, and records taken June 29 and July 11 show waves practically identical with those of this figure.

The very prompt appearance of left ventricular predominance in this patient is difficult to explain on any other theory than the destruction of an appreciable amount of the muscle of the right ventricle. The sector of the heart indicated in Figure 4 can be seen to include left as well as right ventricle, but owing to the fact that the mass relation of the ventricles normally averages about left to right as 2.2 to 1,[6] it follows that an area of necrosis involving parts of both ventricles such as would result from obstruction of arterial branches to the septum, would cause a relative predominance of the left ventricular mass, this predominance increasing greatly for slight increases in the size of the necrotic area even though both ventricles were equally involved.

The more gradual change in the direction of the T wave may go with the more gradual establishment of complete loss of function in the necrotic area, combined with a more gradual restoration of normal function in the tissues at its border by the collateral circulation. The new direction which the T wave has taken on indicates a predominant current within the heart which flows in a direction more from the right toward the left, more from the apex toward the base and more from the lower toward the upper halves of the heart.[4] This is opposite in direction to the current which was flowing during this part of the heart cycle immediately after the injury, and probably depends on the absence of function within the injured area which was at first overactive, so that now the currents due to normal activities in other areas have become predominant. The flow is toward the injured region just as after cooling the muscle with ethyl chlorid. A similar change in the direction of the T wave of the dogs was noticed by Smith to take place twenty-four hours after the onset of the arterial obstruction, and, in fact, many of the records published by him show characteristics similar to the later records of our case shown in Figure 2.

We have, then, seen the form of the human electrocardiogram immediately after the obstruction of a branch of a coronary artery, and the form which it later assumes and maintains for a period of four months. All of the theoretical and experimental evidence which has been mentioned, is seen to be in agreement as to the site of the injured area, and thus tends to support and to prove itself.

6. Lewis, T.: Ventricular Hypertrophy, Especially Preponderance of One or Another Chamber, Heart **5**:367, 1914.

CLINICAL OBSERVATIONS

In order to find whether these observations could be made use of clinically, a large number of electrocardiograms have been gone over, looking for those with the characteristics which appeared in the later records of this patient. Four were found in about 1,000 consecutive records, and to these may be added one record published by Herrick.[7] These five electrocardiograms are shown in Figure 5. The clinical records of all of these cases, but one, included descriptions of typical attacks of anginal pain. This one patient (Case 2) complained of precordial discomfort which was felt on walking during the first hour after meals, and less frequently at other times. Figure 6 shows four other records which were selected because they showed ventricular complexes with characteristics similar to those of our case, but which were evidently not typical. None of these four patients gave histories of precordial pain.

It seems a suggestive fact that precordial pain was present in all of the cases of Figure 5 whose records closely resemble the later ones of our case shown in Figure 2, and was present in none of the cases of Figure 6 whose records do not so closely resemble those of Figure 2. In addition to this, the dogs operated on by Smith showed, after a day or two, electrocardiograms which also had characteristics similar to those of the records of Figures 2 and 5. For these reasons, I believe that when we find such an electrocardiogram from a patient with precordial pain, even of very slight degree, it is proper for us to make the diagnosis of an old obstruction of a branch of a coronary artery. The characteristic features of these records seem to be that the Q R S group is usually notched and usually shows left predominance: the T wave starts from a point near but not directly on the base line, and in one lead, either Lead III or Lead I, quickly leaves it in a sharp curve, as in Lead III of Figure 2, and Lead I of Case 6 in Figure 5, there being no short level stretch before the peak of T as is so evident in normal records; the T wave is usually turned downward in two of the three leads, in Lead II and either Lead I or Lead III; the T wave is usually of large size and accordingly has a sharper peak than usual. Records taken shortly after the obstruction has occurred will not have these characteristics, but will be like that of Figure 1, the typical features being the extreme height of the T wave, and the fact that this wave starts from a point on the Q R S group well away from the base line, denoting that the normal balance of the currents in the heart which should occur at this time, has not taken place.

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7. Herrick, J. B.: Thrombosis of the Coronary Arteries, J. A. M. A. **72**:387 (Feb. 8) 1919.
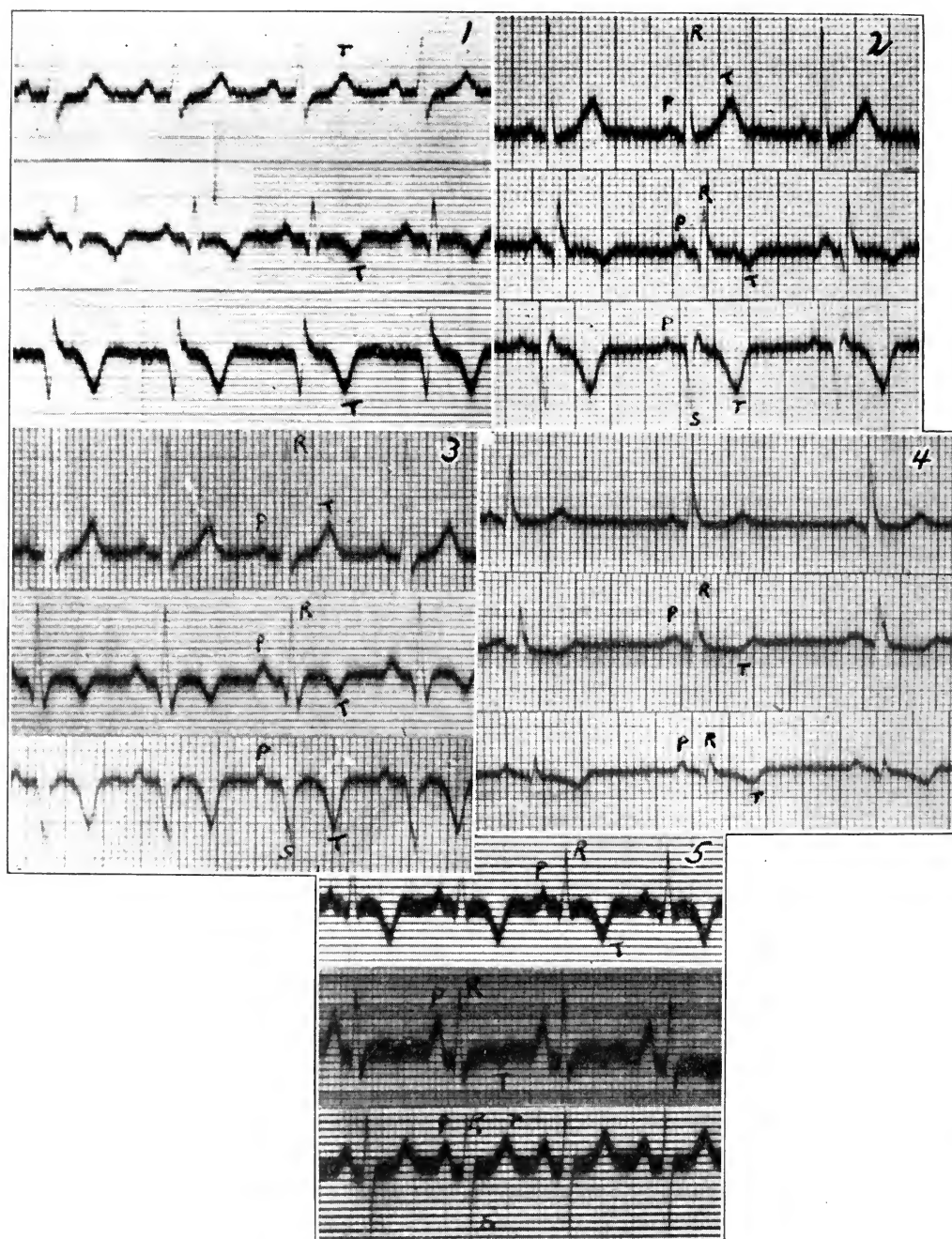
Fig. 5.—Electrocardiogram of five patients, all of which show the changes resulting from former coronary artery occlusion. Record No. 5 is of Herrick's case. (Through the kindness of Dr. Fred M. Smith, who was good enough to send me the prints, I am able to publish this curve and also that of Figure 3 B.)

It is reasonable to suppose that a coronary obstruction may arise gradually by a narrowing of the lumen of the vessel by arteriosclerosis, and lead to the same sort of an area of degenerated muscle as is found some time after the occurrence of an acute obstruction, and that such a case would give the typical electrocardiographic signs. This may account for the fact that Case 2, in Figure 5, shows these signs without having had a severe acute attack such as would accompany an acute obstruction. Further, it is likely that any other disease condition, such as syphilis, which leads to the degeneration of a large localized area of ventricular muscle, would also give an electrocardiographic picture of this sort, for there is nothing special about coronary obstruction in relation to this sign, except the relatively great frequency of its occurrence as a cause for localized areas of myocardial degeneration.

It is true, that not all patients who have attacks of precordial pain show this sign, but this does not prove its unreliability, for there are other causes for attacks of precordial pain than coronary obstruction. It seems likely, also, that a certain minimal area must be involved in order to affect the electrocordiagram in this characteristic way, and that involvement of a lesser area might still cause pain. The only case in which a necropsy was made is that of Herrick, and this heart showed relatively large areas of myosclerosis, one being "4 cm. in diameter" on the outer wall of the left ventricle, and another involving "the wall of the left ventricle near the apex, and the interventricular septum." The apical involvement of the ventricles in this case is of interest in connection with the fact that the T wave of his electrocardiogram (No. 5 of Fig. 5) is caused by a current with a direction opposite to that of the current of the T wave of Figure 2 which has been conconsidered to have the involvement in the basal region of the ventricles.

These signs which have been described may very well not be the only ones which are produced by coronary disease, but I believe that the evidence that they are so produced is reasonably good. They seem to indicate obstruction in the area supplied by the left coronary artery, though this is not conclusively proven. It seems likely, also, to judge from the experimental work which has been mentioned, that some of the electrocardiograms which have the form characteristic of a lesion of the right branch of the auriculoventricular bundle, are, in fact, due to obstruction in the area supplied by the right branch of the coronary artery. Both of the references cited show such records, obtained after lesions affecting this area, and theoretical considerations would lead us to expect this form after such a lesion.

SUMMARY

1. A patient who had just had an attack typical of occlusion of a coronary artery showed a very remarkable electrocardiogram.
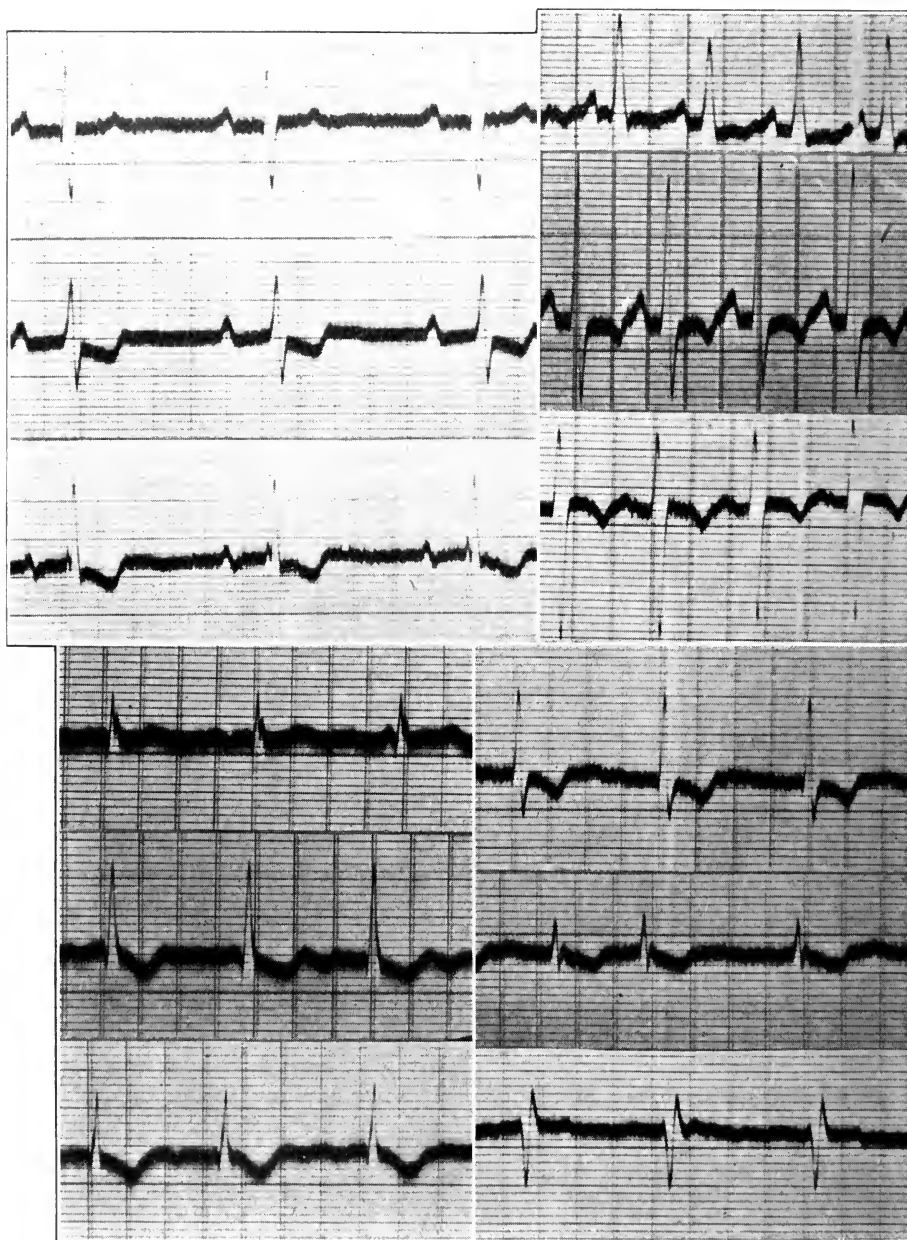
Fig. 6.—Electrocardiograms of four patients, all of which show changes in the ventricular waves but not those typical of coronary occlusion.

2. The patient recovered and the electrocardiogram had changed on the fourth day to a form which it retained for the four months during which he remained under observation. He lived for two years longer, and died with a typical attack of angina pectoris.

3. Five other records have been found which showed characteristics like those of the later records of this patient. Four of these five patients gave a history of typical attacks of anginal pain, while the other had slight precordial pain on exertion. One case, which came to necropsy, showed large areas of muscle degeneration at the apex of the ventricles.

4. The form of the electrocardiogram in these cases is what might be expected on theoretical grounds to result from the occurrence of a fairly large area of degeneration in the ventricular muscle.

5. Experimental work on dogs agrees with the theoretical considerations, and has produced changes in the dogs' records which are similar to those in the case here reported both at the time of the obstruction and later.

6. The characteristic changes appearing a day or two after the obstruction are as follows: The Q R S group is usually notched in at least two leads, and usually shows left ventricular predominance. The T wave does not start from the zero level of the record in either Lead I or Lead III though, perhaps, from a level not far removed from it, and in this lead quickly turns away from its starting point in a sharp curve, without the short straight stretch which is so evident in normal records preceding the peak of the T wave. The T wave is usually of larger size than customary and accordingly shows a somewhat sharper peak. The T wave is usually turned downward in Lead II and in one other lead. Not all of these changes are to be found in every record, but enough of them are present to give it a characteristic appearance.

7. It is concluded that this electrocardiographic sign indicates the presence of a rather large area of muscle degeneration, and when it is obtained from a patient who gives a history of precordial pain coming either in attacks or upon exertion, that it will complete the diagnosis of obstruction of a branch of a coronary artery.

8. It is suggested that this sign results only from a lesion within the area supplied by the left coronary artery, and that one within the area of the right coronary artery would cause changes so that the record would more or less closely resemble that which follows a lesion of the right branch of the auriculoventricular bundle.

BOOK REVIEWS

A LABORATORY SYLLABUS OF CLINICAL PATHOLOGY. By Charles E. Simon, B.A., M.D., Professor of Clinical Pathology in the School of Medicine and the College of Physicians and Surgeons of the University of Maryland, Baltimore. Ed. 1. Cloth. Pp. 86. Philadelphia: Lea & Febiger, 1919.

The author presents this manual for several reasons, which, during his large experience in teaching clinical pathology, have become more and more evident to him. One of the chief reasons for this manual is to give a method whereby the brief half-hour talks by the instructor at the beginning of each period can be eliminated, thereby saving wasted effort on the part of the instructor and providing the student with more time to study and complete the work of each period. The laboratory work has been arranged on the basis of thirty-nine lessons, each lesson to occupy a two-hour period. The subject matter has been arranged in connection with each lesson under three headings, viz.; (1) Instructions to laboratory assistants, regarding material, reagents, etc. (2) Instructions to the student as to method and manner of reports, etc. (3) A set of questions based on the work done in the laboratory and on home reading, which are to be answered in writing at home and presented as part of the work done in the course.

The scope of the work covered is quite extensive, the methods well selected and in general use, and it places the burden of supplying a large variety of material on the instructor, which is as it should be. Most physicians, as well as students, would profit greatly if they could have the opportunity of taking such a course. The book should be found serviceable as a teaching manual, but would be of limited value to the practicing physician.

COLLECTED STUDIES ON THE PATHOLOGY OF WAR GAS POISON-ING. From the Department of Pathology and Bacteriology, Medical Service Section, Chemical Welfare Service, Under the Direction of Major W. C. Winternitz. New Haven: Yale University Press, 1920.

The present volume is the first work published by the Yale University Press on the Anthony N. Brady Memorial Foundation. Three distinct lines of work were undertaken by the Medical Service Section—physiology and toxicology, metabolism and pathology. This thesis represents the work of the last named group.

The studies are presented in a large volume with a profusion of illustrations, many of these done in colors. Indeed one might obtain a very good idea of the effect of poison gases on the air passages and lungs simply by a careful inspection of these remarkable drawings and water colors.

One chapter is devoted to an interesting experimental study of intratracheal therapy. The authors found that perfusion of the lung with large volumes of salt solution is effective in removing such material as India ink, starch paste and bacteria. The experiments suggest the possibility of intratracheal therapy in gas poisoning based on pulmonary irrigation.

Attention is called to the tendency to hemorrhage in the lungs for weeks and months after gassing. The animals that died a violent death showed a higher percentage of hemorrhage than those that died of disease. The authors conclude that a soldier recovered from the acute effects of gassing should be regarded as an individual with damaged lungs and should avoid muscular effort or other practices which might lead to increased blood pressure. Otherwise pulmonary hemorrhages are likely to occur.

This monograph is altogether a most creditable and important contribution to war medicine.

CLINICAL AND ANATOMIC RELATIONS IN CHRONIC NEPHRITIS *

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NEW YORK

The pathologist who is also a clinician finds himself constantly in a state of disillusionment. He finds that many conventions of clinical medicine and anatomic facts do not always coincide, not in the broader sense of diagnosis, but in the finer interpretation of clinical data by pathologic diagnosis and vice versa. After years of such attempts at interpretation he becomes painfully aware that pathology, after all, does not explain everything in clinical medicine, and that in order to bring current medical lore and pathology into closer relationships, many readjustments are necessary. There can be only two such reasons why this should be: either clinical medicine is wrong insofar as clinical data have not been sufficiently "checked up" with anatomic facts in the past; or our pathology is wrong insofar as these facts have been falsely interpreted in terms of clinical medicine. Both these factors are at fault, but the clinician is more to blame because he shifts the entire burden of responsibility for the interpretation of clinical data on the shoulders of the pathologist, who is obviously in no position to interpret them. The pathologist, too, is at fault, not so much because he knows little of clinical medicine, but because in his enthusiasm for pure morphology he is apt to relegate pathogenesis and pathologic physiology into the background of his consciousness. No one who has pondered over these things can fail to realize that a large field for investigation lies in the closer correlation between clinical medicine and pathology. Tradition must be tested by the touchstone of critical observation.

These reflections are the result of studies on nephritis [1] recently published by the writer. In attempting to reconcile traditional clinical medicine with the material obtained at the autopsy table he found that, except with limitations, certain supposed varieties of clinical

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1. Moschcowitz, E.: Hypertension; its Relation to Arteriosclerosis and Nephritis and Etiology, Am. J. M. S. **158**:668 (Nov.) 1919.

nephritis did not correspond with findings at necropsy; and, on the other hand, certain pathologic lesions afforded little more than a pure guess in attempting to predict clinical phenomena. In attempting to interpret these discrepancies the writer drew the following deductions: (1) That in the majority of instances what the clinician means is not "nephritis" but renal insufficiency. In other words, the diagnosis must be couched in terms of function rather than in those of anatomy. (2) That the large group of the so-called "clinical varieties" of chronic nephritis are remarkably indefinite things and have no precise morphological substratum. (3) That so-called various types of chronic nephritis are not end products but stages in a well defined pathogenesis.

1. *Chronic Nephritis Versus Renal Insufficiency.*—Before discussing the nature of these terms certain definitions are in order. The conception that chronic nephritis is a reaction to an injury has not been superseded. This is represented by more or less permanent changes in the organ in which the development of new connective tissue is the predominant lesion. All of the various components of the kidney structure partake in this change. There is no need to describe here in detail the histological characters of chronic nephritis. Briefly, the changes are the following:

(a) The glomeruli: These show a connective tissue change beginning with an increase in the intravascular and the extravascular endothelium [2] of the Bowman capsule, progressing to a connective tissue transformation of these cells, a thickening of the walls of the capillaries, and eventually partial or complete hyaline degeneration of the entire glomerulus, sometimes with calcification. Here I wish especially to emphasize that the process I have briefly described is wholly a vascular change and represents in miniature the same process as that termed "arteriosclerosis" affecting the larger vessels. The significance of this conception will be dwelt on later.

(b) The Epithelium: The epithelium may show no changes whatever. In the more advanced stages, it reveals degenerative changes, often fatty. In advanced nephritides much of the epithelial structure is deformed and destroyed by the encroaching widespread new connective tissue formation. With the destruction of some of the tubules compensatory changes occur in those that remain. There is an apparent proliferation with the formation of adenoma-like masses that

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2. Speculation has been abundant as to whether the lining cells of the Bowman capsule are endothelium or epithelium. Certainly these cells possess all the potentialities of endothelial cells and none of epithelium. In studies upon "Angiogenesis and Ossification (Bull. Johns Hopkins Hosp. **27**:71 (March) 1916), I arrived at the conclusion that the function of endothelium was not specific, but that it could assume all the characters of any cells of mesothelial origin.

contribute greatly to the glandular appearance so often present in advanced nephritides.

(c) The Interstitial Tissue: The changes in the interstitial tissue begin with a slight infiltration of round cells in the cortex, usually in the neighborhood of diseased glomeruli. This is, in all probability, the result of multiple minute infarcts, both of the glomeruli, the arteriae rectae and the larger vessels. In the more advanced stages the round-celled infiltration is more diffusely distributed between the tubules, producing a swollen and whitish appearance of the cortex. In the advanced stages this infiltration has been converted into frank fibrillar connective tissue of varying density. With the scar-like contraction of this tissue and the corresponding atrophy of the intervening parenchyma, there result a thinning and irregularity of the cortex, pitting and indentations on the surface, and, finally, when this scarring involves the organ diffusely, we find the so-called "contracted" kidney. This is the only true end result.

(d) The Blood Vessels: This obviously excludes the glomeruli. In the early stages, the changes may be few or none. In the later stages, the changes correspond to those ordinarily seen in arteriosclerosis of the larger vessels. These changes are too familiar to be described here. In addition to these changes, a passive congestion is an exceedingly common accompaniment, even without a frank valvular lesion of the heart. The significance of this lesion I shall also dwell upon in a subsequent portion of this paper.

Renal insufficiency is an exceedingly complex thing and is consequently not easy to define. The function of the kidneys as a whole, to say nothing of its separate components, is by no means a settled subject: nor are we quite sure to what extent some of the functions that have been attributed to the kidney are purely renal or of extrarenal origin. These are the reasons why it has been difficult to gauge the value of certain functional tests currently employed to test renal insufficiency, so that one must approach the study of renal insufficiency in an extremely critical frame of mind. At all events, some of these tests have proven beyond doubt, by the results of operation, by anatomical findings and otherwise, that they are of value in prognostically estimating renal insufficiency.

I shall not enter at present into a discussion of the relative values of any of these tests. This subject is still in the formative stage and is rich in speculation. In reviewing this work, however, certain facts stand out prominently. 1. That no single test is an adequate guide to renal function, but that a larger number in various combinations must be performed in order to gain an even fair perspective of the renal function. In other words, it is not function but functions that must

be determined.   2. That a single determination of one or various tests gives little prognostic information and indicates only an approximate determination of renal insufficiency at the time at which the tests are performed. To be of any constructive value these tests must be repeated during the entire course of the illness. 3. A corollary of the previous observation: That these tests are profoundly influenced by extrarenal factors. Among the most important of these factors are the following: (a) diet, especially fluid intake; (b) the condition of the patient; whether he is afflicted with a coexisting disease, etc.; (c) changes in the function of some of the other organs, the liver for instance, due either to the direct result of the kidney disease or to circulatory changes consequent upon the renal malady; (d) circulatory insufficiency. This is, in my estimation, the most important factor.

These observations lead one to suspect, what, indeed, proves to be true, that renal insufficiency cannot be estimated, except to a limited extent in terms of the amount or degree of anatomic injury to the kidney. I have for years attempted to correlate the extent and variety of damage of either of the glomeruli and tubules with the clinical findings expressive of disordered renal function, and have thus far failed to determine any precise relationship. In the vast majority of instances, it is true, a lesion of the kidney was found, but one could rarely predict clinically, except within certain limitations, what the extent and variety of the lesion would prove to be. Indeed, it is perfectly possible to find kidneys with little or no injury to the parenchyma, although all the evidence during life indicated impairment, even severe, of the renal function. On the other hand, badly damaged kidneys are often found at autopsy, although the clinical findings during life were normal or nearly normal. This is especially evidenced in the so-called "secondarily contracted kidney" or the "arteriosclerotic kidney" of Sutton and Gull. During life patients who harbor such kidneys reveal little in their urine, except occasionally traces of albumin and a low specific gravity. In such patients Larkin and Levy [3] found normal nitrogen figures in the blood, except just before death. Nevertheless, such kidneys are frequently present as accidental findings; the patient does not die in uremia, as we should expect, but from an intercurrent infection, cardiac failure, arteriosclerosis, etc. These facts explain the futility of all attempts to explain symptoms, urinary findings and other tests of renal insufficiency, including hypertension, etc., on a mechanistic basis. The most recent attempt has been that of Elwyn,[4] but Christian [5] in an admirable critique reveals the fallacies of Elwyn's assumptions.

3. Larkin and Levy: International Clinics, 1918, ii, 26.
4. Elwyn: Am. J. Urol. **3**:47, 1919.
5. Christian: Progressive Med. **24**:119, 1919.

To discuss all the possible relationships of each of the numerous clinical findings and tests for renal function at present at our command would be futile in the light of the inadequacy of our present knowledge of the significance of these tests. I shall, in this place, merely discuss three of the most important, viz., albuminuria, hypertension and albuminuric retinitis.

Albuminuria.—In a previous paper I have already discussed the significance of this symptom and its relation to anatomic damage to the kidney. I tried to show that neither its presence nor its quantity is at all commensurate with the variety and degree of damage to the kidney. Albumin may be present in considerable quantities even when the kidneys are entirely normal, as in orthostatic albuminuria, or in cases of circulatory insufficiency due to valvular heart disease, disappearing when sufficiency has been restored. In both instances, especially the latter, the presence and disappearance of the albumin cannot be explained on other than purely physiologic grounds. On the other hand, albumin may be absent or practically absent, even when the kidney has suffered extensive damage, as in the so-called "contracted" kidney. It apparently makes little difference whether the glomeruli or the tubular portions are involved or both; the presence or quantity of albumin bears little relationship to the amount or degree of damage to the kidney.

I am willing to concede, indeed, I have demonstrated this to my own satisfaction, that albumin is usually proportional to the extent and degree of the tubular degeneration associated with many infections, (e. g., typhoid fever, pneumonia, subacute bacterial endocarditis) the albumin resulting from cell autolysis or increased filterability, but I do not believe that the changes in the tubular epithelium are to any great extent a determining factor in causing albuminuria in the other nephritides, especially of the chronic variety.

These observations leave us no ground for assuming that the kidney is merely a filtering organ, an assumption that physiologists have already amply disproven. The presence of albumin is determined by other factors than mere damage to the glomeruli or the tubular cells. Pressure and volume changes within the blood vessels, the composition of the blood, especially of the threshold bodies [6] and as yet little understood colloid changes in the plasma are equally, if not more, important factors in causing albuminuria, as are pathologic changes within the kidney.

I am fully aware that albumin is probably not the main or even the earliest evidence of renal insufficiency. As Myers and Kilian [7]

6. Cushny: The Secretion of Urine, London, 1917.
7. Myers and Kilian: Am. J. M. Sc. **157**:674, 1919.

have shown, diminished phthalein and increased blood urea and creatinin figures may be found even when albumin is absent from the urine. I simply mean to convey that albuminuria bears no consistent relation to the amount or degree of pathological changes within the kidney, that is, so far as our microchemical methods permit us to determine.

Hypertension.—In the paper already mentioned I submitted the thesis that hypertension was not a consequence of nephritis or arteriosclerosis, but that it was a primary compensatory phenomenon due to unknown causes, and that the nephritis and arteriosclerosis represented secondary changes due either to the hypertension itself or to the cause or causes of the hypertension. I shall not here detail the lines of reasoning that led me to this conclusion; I shall simply say that subsequent observation and reflection have confirmed me in this belief. My conception expressed in terms of clinical medicine is the following: The vast majority of the nephritides or cardionephritides began clinically as cases of so-called "essential" hypertension; i. e., the patient reveals on physical examination a greater or lesser degree of hypertension, greater on the diastolic scale, with or without cardiac hypertrophy, but without evidence of renal insufficiency as apparently evidenced by the absence of albumin or casts. I am not aware at this time of studies that show the status of other tests of renal insufficiency in clinical cases of essential hypertension, but I would not be surprised if such tests showed evidences of renal insufficiency, even though albumin were absent. In any event, if one follows such cases, as I have done, one finds generalized changes occurring in the tissues of the body, especially in the arteries, notably the retinal, the coronaries, the cerebral and the renal.

If arteriosclerosis, the albuminuric retinitis and nephritis are analyzed in their morphologic and genetic aspects, no one, I believe, can escape the conclusion that they are all manifestations of one and the same lesion, a primary vascular productive inflammation affecting all the blood vessels from the capillaries to the aorta. In the kidney, as I have described, and as all authorities are agreed, the primary change is in the glomeruli. This represents the type known as "glomerulonephritis." As the process advances, the larger vessels become affected. All subsequent lesions in the kidney may be traced morphologically from these primary changes in the blood vessels of the organ. Owing to the destruction or impoverishment of the blood supply of focal areas in the kidney, smaller or larger infarcts occur which in turn produce new connective tissue, first in the form of round cell infiltration, and later in the form of fibrillar and hyaline connective tissue. Much of the degeneration of the epithelium can be explained

by the same pathogenesis, although some of it is probably due to waste products from the altered metabolism. The disappearance and malformation of the tubules are accounted for in large measure by the destructive effects of the new connective tissue transformation.

The kidney in chronic nephritis may, therefore, be conceived as a tissue filling the interstices of a framework of blood vessels, depending on the integrity of these blood vessels for its preservation and function. When this framework is injured, the organ, like a house, will fall to pieces. This is the reason why I agree with those who hold that chronic nephritis is a primary vascular disease, e. g., Jores. *Chronic nephritis and arteriosclerosis, therefore, are, to my mind, one and the same lesion.* I believe it is incorrect to view arteriosclerosis, either clinically or pathologically as a disease affecting the larger vessels only. It affects the entire arterial system, from the capillaries to the aorta.

The lesions in chronic nephritis, as a result of this local arteriosclerosis, may be viewed as representing a continuous series of granulomatous changes, and all phases of the morphology may be explained in the light of such changes. The various lesions encountered in chronic nephritis are subject to the identical laws of morphology as apply to granulomatous changes in other tissues from whatever causes. Thus the changes in the kidney are entirely analagous to those witnessed in the various stages of cirrhosis of the liver, or of chronic oöphoritis or in an ordinary granulating wound.

Retinitis.—A more readily grasped analogue, which few appreciate, is the complete identity even down to the minutest details between the lesion of chronic nephritis and those of albuminuric retinitis. Accept any description of the pathological lesion in retinitis, that of Collins and Mayou [8] for instance, and the lesions in both nephritis and retinitis are paralleled in every detail, both in morphology and in the order of their appearance. Indeed, these authors admit that the lesions "are in reality degenerative processes secondary to changes in the retinal vessels." This analogue is, I believe, a strong support for the thesis that the nephritis is not primary but a result of the hypertension: for this type of retinitis as far as my observation leads me to believe, is never present unless hypertension is or has been present, and if the retinitis is sequential to the hypertension or to the cause or causes of the hypertension, it seems to be a logical deduction that the nephritis, which is the identical lesion, cannot but be a consequence as well. It would be an interesting study to see how far the nephritis and the retinitis parallel each other in gravity.

8. Collins and Mayou: Pathology and Bacteriology of the Eye, Philadelphia, 1911.

Depending, therefore, on which organ is most affected a certain clinical picture is developed, which may be that of generalized arteriosclerosis, a localized arteriosclerosis (cerebral arteriosclerosis) apoplexy, aortitis, coronary sclerosis (resulting in chronic myocarditis), and finally chronic nephritis. The patient usually presents himself at a time when the more advanced stages are manifest, but if we observed the real beginnings of the disease, a circumstance, as Mackenzie emphasizes, of fundamental importance in the biological study of disease, I believe that practically all such cases would have revealed the clinical syndrome of "essential hypertension." Certain it is, that the presence or degree of hypertension bears little or no relation to the presence or degree of damage done either upon the arteries or the kidney. Just as we see hypertension often associated with little or no disease of the arteries and profound disease of the arteries (decrescent type of Allbutt) associated with no elevation of blood pressure, so we see increased blood pressure where the kidneys are normal or practically normal [9] (Hirschfelder,[10] Mosenthal [11]) while, on the other hand, normal blood pressure may be present in patients whose kidneys are profoundly diseased. The latter phenomenon is seen not uncommonly in association with the senile or "arteriosclerotic" kidney, a form which corresponds, in my belief, to the decrescent type of arteriosclerosis and is, moreover, indistinguishable morphologically from the contracted kidney resulting from a progressive glomerulonephritis.[12] Indeed, all attempts to correlate these two phenomena have thus far failed, either when we conceive of the destructive process within the organ as a whole, or analyze it in terms of the different components of the kidney structure. This is one of the main arguments I have adduced to support the belief that the hypertension is the primary and the arterial and kidney lesion the secondary phenomenon. Genetically, the hypertension certainly preceded the signs of nephritis in a very large percentage of all cases, as any clinician with experience can testify. Moreover, this belief is supported by the fact that all other chronic nephropathies, morphologically easily definable

9. I have recently acquired two such kidneys in patients in whom the systolic blood pressure was over 200. These will be reported later.

10. Hirschfelder: Diseases of the Heart and Aorta, Philadelphia and London, 1918.

11. Mosenthal: Medical Clin. N. America, July, 1917, p. 101.

12. Vide MacCallum (Textbook of Pathology, 1917): "The gross appearance of such a kidney (arteriosclerotic) differs in no way, therefore, from the end result in a protracted glomerulonephritis (the so-called secondarily contracted kidney), and in all probability something similar may result if the destruction be severe enough and time be given in the case of the tubular and interstitial forms. As a matter of fact, except perhaps through the presence of the strikingly thickened blood-vessels, it is difficult if not impossible to distinguish microscopically the types of ultimately contracted kidney."

from that which I have described, amyloid, subacute bacterial endo-carditis, chronic surgical lesions, experimental destructions, congenital cystic kidneys, parenchymatous nephritis,[13] etc., are never associated with hypertension.

The reason why we cannot predict the variety or degree of changes, in other words, the "type" of kidney that we shall find from clinical findings alone, lies, I believe, in the fact, that these changes or "types" do not represent end products, but only phases of a definite progressive morphologic pathogenesis, so that the "type" of kidney found at autopsy does not represent in any sense the final result, transcribed in reports as the "cause of death", but rather, that particular stage of the disease in which the patient happened to die, whether from an apoplexy or coronary thrombosis or uremia. The nephritis is therefore a glomerular nephritis in the beginning; a diffuse or granular nephritis, which may be white or red or mixed, large or small, in the next stage; and a contracted kidney in the final stage. The only stage that can on morphological grounds be consistently defined as an "end product" is the final stage of such a pathologic process, the so-called "contracted" kidney. Genetically, therefore, it is reasonable to suppose that in the so-called "essential" hypertensions the kidneys present little damage, limited to the glomeruli where the early changes in chronic nephritis originate; while in the hypertensions in which renal functional tests show a profound insufficiency the damage to the kidney is diffuse and extreme. I cannot state this with any reasonable degree of exactitude, because both my experience and the reported observation are inadequate. The difficulty is that patients with "essential" hypertension do not often die in that stage.

The evidence which I have presented is sufficient, I believe, to demonstrate that it is extremely hazardous to predict the amount and degree of damage in the kidney by clinical findings alone. It now remains to determine, if possible, the factor or factors that cause this discrepancy. Not being anatomic, the factors must be physiologic. This is necessarily so, because productive inflammations never completely disappear.

I am convinced that by far the largest factor or rather the largest common denominator of the entire problem is circulatory insufficiency. No one who has seen anything of the clinical phases of "chronic nephritis" can fail to be impressed by the dominating rôle of circulatory insufficiency from the very beginning of the malady to the end. In the earlier stages, whether we view it in the light of a compensatory mechanism or not, this insuffiicency is manifest in a more or less persistent hypertension, with a resulting hypertrophy of the left ven-

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13. Epstein: J. A. M. A. **69**:444 (Aug. 11) 1917.

tricle. In the further course of the disease, other evidences of a progressive circulatory failure arise. These are increased rapidity of the heart action, disturbances in rhythm (gallop rhythm, extrasystoles, auricular fibrillation) and signs of stasis (enlarged liver, hypostasis, edema of the ankles, etc.). If coronary sclerosis occurs, with resulting fibrotic changes in the myocardium due to the blocking of the terminal branches of the coronary vessels, all signs of a real anatomical myocarditis become manifest. In addition to those already mentioned, two very important signs now appear. The first is a lowering of the blood pressure; the second is a change in the electrocardiographic tracing, described by Oppenheimer and Rothschild [14] as "arborization block." During this stage of the illness, which may be described as the middle phase, the patient is responsive to digitalis, and this, despite the fact that the hypertension may not be influenced to a considerable degree; so that by the continuous administration of this drug we are able to keep the subjective and objective evidences of circulatory insufficiency at a certain level; the circulation, in other words, may be said to be compensated. When the signs of circulatory insufficiency increase (decompensation) an increase in the quantity of digitalis combined with bodily rest usually suffices to restore the patient to his previous condition. Finally, it is noted that the attacks of decompensation increase in severity, frequency and duration. All the signs of a grave circulatory insufficiency ensue; the patient no longer responds to circulatory "stimulants" and unless his life is cut short by an apoplexy or an attack of angina pectoris, he dies from a pure circulatory failure or from uremia.

I have used the term "circulatory insufficiency" in a rather broad sense, for I am fully aware that this term comprises many elements aside from blood pressure, changes in rhythm, etc., such as myocardial tonus, blood velocity, volume flow and the viscosity of the blood, but until further investigation enlightens us on the relative importance of these elements in bringing about circulatory insufficiency, we must depend on a clinical concept of this phenomenon.

At all events, the similarity of the circulatory insufficiency noted in the nephritides associated with hypertension and that witnessed in frank valvular disease of the heart is striking. They parallel each other closely not only in signs and symptoms but also in the sequence of clinical events and their response to treatment. The same laws of cardiodynamics apply to both. Furthermore, there is one lesion representing circulatory insufficiency common to both, namely, congestion (Stauung) of the internal viscera. This is shown in brown induration of the lungs, nutmeg liver, chronic congestion of the spleen and

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14. Oppenheimer and Rothschild: J. A. M. A. **69**:429 (Aug. 11) 1917.

cyanotic kidneys. These lesion I have found exceedingly common in autopsies upon cases of "chronic nephritis." The point I wish to bring out is that clinically tests for renal insufficiency are usually coordinate with evidences of circulatory insufficiency, and that the functional state of the circulation has a greater effect in increasing or decreasing the evidences of renal insufficiency than perhaps any other factor.

Not all the conventional functional tests are affected in this manner; I refer especially to quantity of urine, albumin, phthalein, urea and nonprotein nitrogen. Creatinin, uric acid and salt are not so readily affected. The figures rise and fall depending on the condition of the circulation. When the heart action is good, the figures approach normal, and conversely, when it is bad; just before death the figures show the widest variation from the normal.

These observations, it seems to me, receive a strong corroboration from what we find in cases of circulatory insufficiency due to pure valvular disease in which a genuine anatomic nephritis can definitely be excluded. We all know that in mild compensated valvular lesion of the heart, tests for renal insufficiency usually reveal normal findings. We also know that when signs of myocardial or, perhaps, better said, circulatory insufficiency develop, signs of renal insufficiency manifest themselves. There is oliguria; albumin and casts appear, phthalein excretion is reduced, and the blood urea nitrogen figures are above normal. When compensation is restored by rest and digitalis, these promptly disappear. Very often patients exhibit evidences indicating a combination of cardiac and renal disease so that there may be doubt as to how far the malady is cardiac or renal. With the improvement in the condition of the circulation, all signs of renal impairment disappear. If they do not completely disappear we may accept this as evidence that either complete compensation is no longer possible, or, less likely, that an associated productive renal lesion is present.

Observations of Rowntree, Geraghty and Fitz [15] are extremely important as confirming this view. They found in moderate experimental congestion of the kidney, that the excretion of salt, iodid and lactose may be interfered with. The excretion of the phthalein may be normal, but if the congestion is extreme, it may be decreased. "Therefore, in experimental congestion, functional pictures indistinguishable from those of mild or advanced nephritis without cardiac decompensation have been found. The gradual amelioration of experimental congestion is accompanied earliest by an increased phthalein output, later by improvement in salt and iodid excretion, and lastly by a slight amelioration of the delayed lactose excretion." Rowntree

15. Rowntree, Geraghty and Fitz: Arch. Int. Med. **2**:258 (Aug.) 1911.

and Fitz [16] found that clinically cases of passive congestion behaved in a similar way.

These observations, it seems to me, render the examination for renal insufficiency of little value when made during the attacks of decompensation. For purposes of prognosis such tests, as Christian insists, should be made in the interval.

Anatomic Varieties of Chronic Nephritis.—From the foregoing discussion it may be gathered that clinical findings offer little or no basis for furnishing a classification of the forms of chronic nephritis that I have described. This form has received a host of names in textbooks; glomerulonephritis, productive nephritis, diffuse nephritis, interstitial nephritis, arteriosclerotic disease of the kidney, arteriocapillary fibrosis, primary and secondary contracted kidney, etc. Each of these names conveys some aspect of the pathology, but in order to obtain an adequate concept, which must include the origin, spread and progress of the disease, the structures involved and the physical characters of the diseased organ, all of these adjectives would be necessary as prefixes. No single name or group of names can suffice. It seems to me that the term "arteriocapillary fibrosis," devised by Gull and Sutton, is the most applicable. However, it may be taken for granted that none of the methods of clinical examination at our command can enable us to foretell whether we shall find such a kidney in the stage of a glomerulonephritis or that of the large or small red kidney, or the granular kidney or the contracted kidney. All that we have the right to say is that we shall find a kidney of this particular type. It has seemed to me from the few observations I have made, that the longer the duration of the disease, the more progressive the lesion. This is certainly a reasonable expectation.

The one unfailing clinical finding associated with this form of nephritis is hypertension. No other nephropathy is associated with this phenomenon. There are two exceptions to this rule. (1) Cases that have developed coronary sclerosis with symptoms of angina pectoris. The resulting fibrous myocarditis causes such an insufficiency of the heart muscle as to apparently neutralize the increased peripheral resistance. Anamnesis of such patients reveals the interesting fact that previously, perhaps a year or two ago, the blood pressure had been considerably elevated. I have a number of records of such cases. I have seen one case of angina pectoris in which this decrease occurred under my observation. In another, the associated interstitial myocarditis was proved by autopsy. (2) Cases of "decrescent" nephritis. I call this variety decrescent because it clinically corresponds to the decrescent arteriosclerosis of Allbutt. These patients reveal at

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16. Rowntree and Fitz: Arch. Int. Med. **2**:258 (Aug.) 1911.

necropsy extensive general arteriosclerosis and the so-called "arterio-sclerotic" or "senile kidney" or the "arteriocapillary nephritis" of Sutton and Gull. As Allbutt has pointed out in connection with the decrescent arteriosclerosis, so in this form of nephritis there is no hypertrophy of the left ventricle, and it is the exception rather than the rule for these patients to die from the causes common in the diseases of the hypertensive type.

The other sign characteristic of the hypertensive type of nephritis is an albuminuric retinitis. As far as I am aware, this type of retinitis is practically always associated with hypertension either present or past.

There are, however, other chronic nephropathies with different genetic and morphologic characters of their own, which while offering many of the signs and symptoms of the hypertensive type, yet possess certain symptoms and findings sufficiently characteristic to render them clinical entities as well. Most of the tests for renal insufficiency are common to both.

I shall exclude for obvious reasons the chronic surgical and specific nephropathies.

There remain for discussion the following varieties of chronic nephritis:

1. *Parenchymatous nephritis or nephrosis (Epstein).*—Although pathologic studies of this variety of nephritis are still lacking, it seems necessary, because of its clear cut clinical characteristics, to recognize this malady as of an entirely different type from the foregoing. This type of nephritis is a disease of youth or middle age. The urine is usually diminished in amount, rich in normal solid constituents and in albumin and casts. Edema and anasarca are early and prominent symptoms. But the most characteristic findings, according to Epstein, are the impoverishment of protein in the blood plasma, with an increase in the globulins, and a relative or absolute increase in the lipoid and cholesterol bodies. Epstein has obtained excellent results in this variety of nephritis by a diet high in protein and low in fats.

2. *Chronic glomerulonephritis associated with subacute bacterial endocarditis (Streptococcus viridans).*—While in the literal sense this lesion is not a chronic one, except in the healed stage, it is included in this discussion. This variety was first described by Löhlein [17] and more recently by Baehr.[18] The lesion according to Baehr is characteristic of subacute bacterial endocarditis and occurs in no other hematogenous bacterial infection. The lesion is a progressive one, is limited strictly to the glomeruli, and consists in swelling, degeneration and desquamation of the cells of Bowman's capsule, later followed

17. Löhlein: Ueber die entzündlichen Veränderungen der Glomeruli be i menschlichen Nieren und ihre Bedeutung für die Nephritis, Leipzig, 1906.
18. Baehr: Proc. New York Path. Soc., December, 1911.

by fibroblastic changes in the capsule and eventually (in the healed stages) by hyalinization of this mass. The new connective tissue formation never proceeds beyond the confines of the glomerulus. This lesion affords to my mind a convincing refutation of the argument of those who regard a glomerulonephritis as the primary cause of a hypertension.

Viewing the renal lesion separately, aside from the associated cardiac lesion, the one clinical finding characteristic of this lesion is hematuria which is fairly constant. If the bleeding is not macroscopic it is microscopic.

3. *Amyloid kidney.*—An amyloid kidney is a manifestation of general amyloid disease. The amyloid, greater or lesser in amount is deposited almost entirely in the blood vessels, in the glomeruli, the arteriae rectae and the larger vessels. Usually, there is a profound fatty or lipoid degeneration of the tubular cells; occasionally the amyloid is deposited in a kidney the seat of a widespread connective tissue change.

Hypertension, hypertrophy of the left ventricle and retinitis are absent in amyloid disease of the kidneys. As a rule, the urinary findings are fairly characteristic. The urine is light in color and of a low gravity; albumin is plentiful, and casts especially of the waxy variety are fairly abundant. The nephritic signs are usually so overshadowed by the underlying general condition, usually tuberculosis, that they play a small rôle in causing the death of the patient. Such patients die, as a rule, from cachexia.

CONCLUSIONS

1. Clinical findings in nephritis cannot be interpreted in terms of morphologic pathology, except to only a very limited degree. This is due to (a) various extrarenal factors; (b) to the fact that the "type" of the kidney as found at necropsy does not represent an end product but a stage in a fairly well defined pathogenesis. The lesion begins as a glomerulonephritis and all subsequent stages down to the contracted kidney can be traced and are explainable, according to established genetic and morphologic criteria, from this lesion.

2. Thus the conception is set forth that chronic nephritis is essentially a vascular disease, beginning in the capillaries (glomeruli) and extending therefrom to the larger blood vessels. The term "arteriocapillary fibrosis" devised by Sutton and Gull, appears to fit the nature of the malady better than any in current use. In this light chronic nephritis and arteriosclerosis are one and the same lesion. Arteriosclerosis is conceived not as a disease affecting only the larger vessels, but of the entire arterial system from the capillaries to the aorta.

3. The lesions in albuminuric retinitis are analogous morphologically with those of chronic nephritis. This analogy and the sequential relation of albuminuric retinitis to hypertension is a strong argument in favor of the previously submitted thesis that nephritis is not the primary cause of hypertension but is a secondary consequence to the hypertension itself or of the cause or causes (unknown) of the hypertension.

4. The presence or extent of albuminuria bears no consistent relationship to the degree or variety of anatomic destruction of the kidney. Physiologic conditions are more important factors in causing albuminuria than anatomic disturbances in the kidney.

5. The presence or degree of hypertension bears no consistent relationship to the degree or variety of anatomic destruction of the kidney. The probability is very strong that *clinically* cases of chronic nephritis begin as cases of "essential hypertension." If patients with essential hypertension are followed over a long period of time there progressively develop the clinical evidences of either a generalized arteriosclerosis, a localized arteriosclerosis (cerebral endarteritis, coronary sclerosis, albuminuric retinitis) or a renal arteriocapillary fibrosis (chronic nephritis) or a combination of these.

6. The only variety of chronic nephritis that can be reasonably termed an end result is the so-called "contracted" kidney. The contracted kidney arising from a chronic glomerulonephritis (secondary contracted kidney) is morphologically indistinguishable from the "primary contracted" kidney. A "contracted" kidney may be unassociated with hypertension, left ventricular hypertrophy or evidences of renal insufficiency. In such instances, the patient does not die a "renal" death. This kidney is termed the "decrescent" kidney since it corresponds clinically to the "decrescent" variety of arteriosclerosis described by Allbutt.

7. The most important extrarenal factor in modifying renal insufficiency in "arteriocapillary fibrosis" is circulatory insufficiency. Other things being equal, improvement in circulatory insufficiency is coordinate with improvement in renal insufficiency, and vice versa.

8. There is a striking parallelism between the signs of renal insufficiency in arteriocapillary fibrosis associated with hypertension and those noted in frank valvular lesions of the heart. Decompensated phases of valvular heart disease may show evidences of renal insufficiency indistinguishable from those witnessed in chronic nephritis.

9. As a consequence of these studies the following clinical pathologic classification of chronic nephritis is submitted: 1. Arteriocapillary fibrosis. 2. Chronic glomerulonephritis of subacute bacterial endocarditis. 3. Amyloid kidney. 4. "Chronic parenchymatous nephritis" or nephrosis (Epstein).

A CASE OF MASSIVE LIPOMA OF THE MEDIASTINUM

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The presence of a lipoma in the anterior mediastinum, weighing 17 pounds 6 ounces, is so unusual that I wish to record my notes of a case in full.

REPORT OF CASE

R. K. B., aged 37⅓ years, American; clergyman; married. Family history negative. Aside from diseases of childhood, patient was a healthy child and an athletic boy. At 16 he was kicked in the abdomen by a horse, and his recollection of this was a feeling of distress, at times, for about one year. Never had an injury of the chest; never had pleurisy, pneumonia or pericarditis. He had a deep cough, similar to the one developed with the last illness, about five years before, lasting about a month.

Present Illness.—Patient was well until about seventeen months ago when he sought medical advice for a deep, hollow cough which appeared while in apparent physical fitness. Gradually, this cough became more persistent and was referred to the throat, just above the sternum, described as of an irritating character. Color was good, no constitutional symptoms, no laryngeal symptoms, but an occasional deep sigh and a sensation of a slight substernal oppression. In about four months this amounted to shortness of breath and an occasional wheezing. He slept quietly and well, preferably on the left side, with little or no cough at night.

During the next five months the cough and dyspnea grew rapidly worse and with it a beginning feeling of heaviness in the chest, and exertion was accompanied by an alarming dyspnea. It became necessary to sit upright, or leaning forward. Almost constantly leaning forward; he could not lie on his back. Weight loss, 10 pounds.

At nine months, roentgen-ray treatment being instituted, his condition seemed to improve for a few weeks, but while his cough became less harassing, the dyspnea and oppression again returned and increased. He grew weaker and thinner in the face and arms, slight edema of the lower limbs appeared, and he could sleep only in the knee chest position, while the slightest exertion produced painful attacks of respiratory embarrassment.

By the fifteenth month he had to lean forward resting his chest on a table constantly, the air-hunger was continuous. The edema of the lower extremities, genitalia and abdomen was extreme. Marked cyanosis of the upper extremities and especially the head appeared; later, numbness of the arms, mental torpor, and finally, a distressing struggle for air preceded a mechanical death.

REPORT OF ROENTGENOGRAPHIC EXAMINATION OF THE THORACIC CAVITY

This examination was made at nine months by Dr. Walter C. Barker. His report was as follows:

The anteroposterior view shows a shadow of greater density than normal, extending from the third rib to the diaphragm. This shadow fills the whole breadth of the chest, except a small area of the lower right side. The lateral view shows a dense shadow with a smooth and sharp outline, bulging the anterior wall of the thoracic cavity and extending downward and backward from the third rib to the diaphragm. At the broadest part it almost reaches

posteriorly to the spinal column. The heart shadow is pushed downward and backward, and the lung shadow is mostly above, with a small air space showing below.

Diagnosis: Large primary tumor in the anterior mediastinum.

The record of early physical signs are unobtainable. A persistent hollow cough, increasing in severity and accompanied by an occasional shortness of breath, and later a pronounced dyspnea, constitute the earliest referable symptoms. Yet at nine months, physical examination

Fig. 1.—Anteroposterior view of chest showing a large tumor. The dark shadow in the lower part of the thorax is cast by the heart; the light shadow at the right and above at the apices is cast by the lungs.

and roentgen-ray examination demonstrated a tumor filling about four-fifths of the chest. There was no pain, no positive emaciation or cachexia, no metastasis, no dysphagia, no aphonia.

Necropsy.—A necropsy was made five and one-half hours after death. Rigor mortis absent. Well developed body, but head and arms thin and of a dusky

bluish hue. Remainder of body extremely edematous. Lower extremities water logged and of twice their normal size. Thoracic cavity: pressure increased, entire cavity apparently filled with an indefinite, lobulated mass conforming to the thoracic arch and extending from the apex to the diaphragm. This mass seems to be attached only at one point, just below the sternal notch, and by only a frail strand of loose adhesivelike bands, easily dissected free with the fingers. The base and posterior surface being found free, the entire

Fig. 2.—Lateral view of chest; shows the shadow of the tumor filling a large part of the thorax. The lungs are crowded above and behind the tumor, and the heart is pushed back and below; the growth being in the anterior mediastinum.

mass is easily delivered, disclosing the heart vessels and lungs compressed along the vertebral column and low in the posterior mediastinum. The heart is very small and pale, measuring approximately 7 by 8 by 6 cm. Lungs measure approximately, 5 by 15 by 3 cm., very dark, and of a liverlike con-

sistence with little crepitation. The peritoneal cavity is filled with a pale transudate, while all the abdominal viscera exhibit extreme degrees of passive congestion.

Pathologic Findings.—A sharply defined, soft fluctuating tumor, covered by a dense tough fibrous capsule which seems to divide it into multiple rounded lobules. On cross section it is apparently a mass of pale yellowish, greasy, fatty tissue. Weight, 17 pounds 6 ounces, measuring 31 by 30 by 15 cm. The anterior surface is convex conforming in general outline and appearance to the thoracic concavity, narrowed at the apex and broad and squatty at the base, with a broad notch midway of the base. The posterior surface is irregular in outline with a vertical concavity about midway, approximately 15 cm. wide at its widest point and about 8 cm. deep. This concavity, which housed the heart, vessels and lungs, is more or less completely lost at the apex while fusing with the notch at the base. All fresh sections stained with sudan III a uniform deep red with few fine grayish stripings of connective bands. The entire tumor developed and fixed well in Kaiserling.

Microscopically, the tumor is composed entirely of masses of fat cells lying in a vascular connective tissue matrix. The individual cells in general are
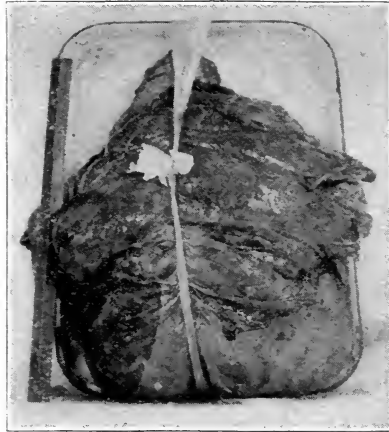
Fig. 3.—The tumor after removal at necropsy, supported against a waiter with a 12-inch ruler standing beside it.

larger than usual fat cells and are round or oval, although in sections taken from about the base they are compressed and flattened. All sections stain perfectly with osmic acid—sudan III.

Medical literature reveals a surprising scarcity of contributions of primary tumors of the mediastinum.[1] While occasional records of teratoma,[2] dermoid,[3] cysts,[4] fibroma and others tumors[5] appear. I have been able to find only four cases of lipoma reported.

1. Behrens: Weekly Bull. St. Louis M. Soc. **139**: 1911.

2. Atlas: Allg. Wien. med. Ztg., 1894. Becker: Internat. Clin. **19**: 1919.

3. Godlee: Proc. Roy. Med. Soc., London, 1908. Kaestle: München. med. Wchnschr. **1**: 1909.

4. French: Proc. Roy. Med. Soc., Lond., 1907. Blackader: Arch. Pediat. **28**: 1911. Rose: Lancet **2**:1308, 1893.

5. Hare: Mediastinal Disease, Philadelphia, Lea & Febiger, 1889. Edwards: Arch. Pediat. **6**:1889. Roberts: Lancet **2**: 1912. Nichols: Boston M. & S J. 1897.

Beatson [6] records having removed a lipoma of about the size of an orange from the superior mediastinum of a man, aged 45. This presented just above the manubrium sterni and had been increasing slowly for five years, but was not causing any inconvenience. Hare [5] collected three cases, of none of which was he able to obtain a thorough description. All patients were males, the ages of two were given as 38 and 50. In one case the tumor was specified as located in the anterior mediastinum. All patients had marked dyspnea. One patient had marked cyanosis of the face. In two cases the pericardium was involved. The duration of one case is given as a little more than one month. All patients died.

6. Beatson: Glasgow M. J. **1**:57, 1899.

NARCOTIC DRUG ADDICTION

I. THE FORMATION OF PROTECTIVE SUBSTANCES AGAINST MORPHIN [*]

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The importance that has been attached to the problem of drug addiction in the past several years has prompted us to make a critical study of certain of its phases. While a considerable amount of experimental work has been done on the subject, it has not been wholly satisfactory in that the conclusions have been either conflicting or uncorroborated.

The first phase of the subject we undertook to study was the question as to whether the continuous taking of morphin causes the presence in the blood serum of any substance which has a protective effect against morphin.

LITERATURE

In 1897, Gioffredi,[1] an Italian, published results of experimental work on alkaloidal immunization, in which he stated that while it was impossible to obtain immunity against the effects of cocain and atropin he was able to obtain a serum from a morphin tolerant dog which protected a second dog from almost twice the fatal dose of morphin. Gioffredi[2] published a second paper in 1899, in which he reports further experimental work on the subject. He established a high degree of tolerance in a dog (a tolerance which enabled the animal to withstand three times the minimal fatal dose of morphin), injected the serum of this dog into young cats and determined the degree of protection afforded by it against morphin. His figure for the minimal fatal dose of morphin hydrochlorid in young cats by peritoneal injection is 0.05 gm. per kilogram weight of animal. Ten c.c. of the serum given intraperitoneally protected cats against doses of from 0.05 to 0.07 gm. per kilogram given not more than two hours before the serum, from 0.08 to 0.1 gm. given not more than one hour before the serum, and from 0.11 to 0.13 gm. given from fifteen to thirty minutes before the serum. If the serum was given before the morphin, death did not occur from doses of from 0.05 to 0.14 gm. per kilogram and this he claims to be true even when the serum is administered as long as from ten to fifteen days before the morphin.

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[*] From the Department of Pharmacology, University and Bellevue Hospital Medical College.

1. Gioffredi: Arch. ital. de biol. **28**:402, 1897.
2. Gioffredi: Arch. ital. de biol. **31**:398, 1899.

Hirschlaff [3] appears to have confirmed to some degree Gioffredi's work. He established a tolerance for morphin in rabbits, and used their serum as a protective substance, employing mice to measure the degree of protection afforded. A study of his tables shows that he considers a dose of from 0.0005 to 0.0007 gm. of morphin per gram weight of mouse as an effective fatal dose. In one series of mice given 1 c.c. of normal rabbit serum, he found no change in his fatal dose. In another series of twenty-one mice treated with 1 c.c. of serum of tolerant rabbits and given doses of morphin varying from 0.0005 to 0.00145 gm. per gram weight, he found that all lived. Some of the serum used to test the protective effect was taken from rabbits just after receiving their last dose of morphin, and some from rabbits which, after acquiring a tolerance, had been deprived of morphin for as much as four weeks before the blood was drawn. There was no difference in the protective effect between the two sera.

Morgenroth,[4] in 1903, pointed out that the dose assumed by Hirschlaff to be a fatal dose is incorrect. Using much greater exactitude in his work he found the fatal dose to be 0.00086 gm. of morphin hydrochlorid per gram of mouse for mice weighing less than 15 gm. In mice over this weight, a dose of 0.00093 gm. per gram of mouse was necessary. He next fixed the fatal dose for mice which twenty-four hours previously received 1 c.c. of normal serum as being 0.0011 gm. per gram of mouse. Finally, after having established the new fatal dose, he tested the protective effect of the serum of rabbits, goats and dogs in which he had established a high degree of tolerance for morphin. From the results on a large series of carefully controlled experiments he definitely concludes that this serum does not possess any specific protective effect.

In 1903 Cloetta [5] brought forth the fact that animals tolerant to morphin lose their tolerance very quickly after withdrawal of the morphin. He states that pigeons and rats accustomed to tolerate 0.15 gm. of morphin without the occurrence of symptoms will succumb to these same doses as soon as two days after the withdrawal. He considers this fact to be in direct conflict with Hirschlaff's findings since one might presuppose that animals whose serum retains the high degree of protection described by Hirschlaff, even four weeks after the withdrawal of the morphin, would be able to preserve their own immunity for at least two days. In order to convince himself whether it were not possible that other substances are formed, direct by-products of morphin, having physiologic antidotal powers, he performed a series of experiments. He poisoned animals with very

3. Hirschlaff: Berl. klin. Wchnschr. **39**:1149, 1177, 1902.
4. Morgenroth: Berl. klin. Wchnschr. **40**:471, 1903.
5. Cloetta: Arch. f. exper. Path. u. Pharmakol. **50**:453, 1903.

large doses of morphin with the hope of obtaining a correspondingly strong antidotal formation, and then used the serum of these animals on mice for the purpose of immunization. Dogs and rabbits were given intravenously large toxic doses of morphin hydrochlorid and after varying periods of from two to seven hours after the last dose, the animals were killed, and the blood drawn and the serum was collected. This serum was then injected into mice in doses of 1 c.c., followed in about twenty-four hours by toxic doses of morphin hydrochlorid. His results show that no such antidotal substance is formed.

Mirto[6] in 1905, in a series of experiments on precipitin reactions using the serum of tolerant rabbits and the various salts of morphin, reaches the conclusion that specific precipitins are not formed.

In 1907, von Marikovszky[7] reported that, after reviewing the work of Hirschlaff and Morgenroth, he thought that a dose of 20 mg. per mouse should be absolutely fatal, but on testing one mouse was astonished to find that the animal survived. From this he assumed that a dose of 30 mg. was the necessary dose. He injected three mice with 30 mg. morphin and followed this with an injection of serum of a rabbit tolerant to morphin (the dose of serum injected is not given). A control mouse received only the 30 mg. of morphin. All the mice died, the only difference being that the serum treated animals survived the control by a few hours. He then experimented with guinea-pigs and found the fatal dose to be 0.07 gm. per 100 gm. weight of animal. In studying his results on the protective effects, we find that the dose of morphin given ranged from 0.07 to 0.116 gm. per 100 gm. and the dose of serum from 1 to 10 c.c. His conclusion as to the protective effect is based on the fact that the serum treated animals survived the controls by periods varying from two to four and one-half hours.

Berri and Belgrano[8] in 1911 claim to have established an agressin and also an anti-aggressin, the latter capable of producing immunizing bodies for cocain and morphin. In their experiments on morphin, they determined the minimum fatal dose of morphin hydrochlorid for rabbits to be 0.41 gm. per kilogram by intraperitoneal injection. Their aggressin was prepared by injecting into the pleural cavities of a rabbit an emulsion of aleuronat followed in about ten hours by morphin hydrochlorid in the dose of 0.20 gm. per kilogram. After from twelve to fourteen hours they aspirated the exudate said to contain the aggressin. From this point they subdivided their work into four series of experiments. In the first series they injected subcutaneously three rabbits with 5 c.c. of the exudate, followed in fifteen minutes by

6. Mirto: Arch. farma. sper. **4**:406, 1905.
7. Von Marikovsky: Zentralbl. f. Bakteriol. u. Parasitenk. **43**:494, 1907.
8. Berri and Belgrano: Annali dell Instituto Maragliano **5**:42, 1911.

0.36 gm. morphin hydrochlorid per kilogram intraperitoneally. The animals all died within a period of three and one-half hours. As controls they injected three rabbits with 0.39, 0.41 and 0.415 gm. per kilogram doses of morphin (without the exudate), respectively. The results were that the first animal lived while the other two died in fourteen and ten hours, respectively. Another animal received 7 c.c. of the exudate alone, and remained alive without presenting any signs of poisoning. From this they conclude that they have obtained an aggressin.

In the second series they studied the immunizing properties of the aggressin itself. They prepared three rabbits by giving each five subcutaneous injections of the aggressin in increasing doses from 3 to 6 c.c. at intervals of from four to five days. Five days after the last dose of aggressin, an intraperitoneal injection of morphin was given, the doses being 0.415, 0.42 and 0.43 gm. per kilogram, respectively. All the rabbits showed toxic effects of the morphin, the first two recovering while the one receiving 0.43 gm. per kilogram died in forty-eight hours. A control rabbit received 0.41 gm. per kilogram of morphin and died in fifteen hours.

The third series shows a study of the protective effect of the serum of rabbits immunized with five injections of increasing doses of the aggressin as in the preceding experiment. Five days after the last dose the animals were bled and the serum collected. Three rabbits were given subcutaneously 10 c.c. of this serum followed in twenty-four hours by 0.415 gm. per kilogram morphin in one of the rabbits and by 0.42 gm. per kilogram in the remaining two rabbits. The first rabbit lived indefinitely, the remaining two died in five and seven days, respectively. A control receiving 0.41 gm. per kilogram morphin died in fifteen hours.

The last series of experiments were performed to show the production of anti-aggressin substances in rabbits. Three rabbits were injected subcutaneously with serum of rabbits immunized against aggressins, two receiving 10 c.c., and one 60 c.c. After twenty-four hours, a subcutaneous injection of 5 c.c. of aggressin was made and followed in fifteen minutes by intraperitoneal injection of morphin in doses of 0.36, 0.37 and 0.37 gm. per kilogram, respectively. All showed toxic effects but recovered. A control receiving 5 c.c. of agressin plus 0.36 gm. per kilogram of morphin died in three hours.

Von Egmond [9] in 1911 and also Van Dongen [10] in 1915 show that morphin tolerance is partially selective in character. Certain parts of the central nervous system (the vagus center) and the gastro-

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9. Von Egmond: Arch. f. exper. Path. u. Pharmakol. **65**:197, 1911.
10. Van Dongen: Arch. f. d. ges. Physiol. **162**:54, 1915.

intestinal tract do not show the same degree of tolerance as do the brain cortex, the vomiting center or the respiratory center. In fact, in dogs tolerant to 1 gm. of morphin it was possible to change the heart rate from 120 to 80 per minute by a dose of 0.04 gm. Doses as small as 0.00004 gm. per kilogram in these same animals showed an appreciable effect.

<div align="center">EXPERIMENTAL WORK</div>

In our work we made use of serum from two sources, first from humans addicted to morphin, and secondly from dogs which were made tolerant to morphin. In the case of the human serum, the blood was drawn while the person was still addicted, and as long as possible after the last dose of morphin. In either case the blood was drawn, allowed to clot and the serum separated by centrifugalization. The serum was injected into the animals as soon as possible after the drawing of the blood.

In setting forth these experiments we subdivide them, for convenience, into two large groups: (1) the effect on mice, and (2) the effect on cats. We chose mice and cats especially as the most suitable animals on which to determine the protective effect of the serum because most of the previous work had been done on these animals.

Group 1 : *Mice.*—Our first attempt was to repeat some of the work appearing in the literature, but after a number of trial tests on mice we found it essential to determine to our own satisfaction the minimal fatal dose of morphin sulphate per gram weight of mouse. Anyone who has worked on the determination of a definite minimal fatal dose of a drug must recognize the inherent difficulties of the problem. Differences in the susceptibility of individual animals, errors in technic, differences in the rate of absorption of the injected poison, render it impossible to obtain a figure which truly represents the actual minimal fatal dose, that is the smallest dose which will invariably cause death.

These difficulties became so apparent in the course of our work, some mice surviving a dose of 1 mg. per gram, while others succumbed to 0.2 mg. per gram, that we finally decided to ascertain the dose that would kill a majority of mice, and base our conclusions on a comparison of the percentage of fatalities from such a dose with and without the serum. The words "minimal fatal dose," used hereafter, mean such a dose.

In performing the tests for the minimal fatal dose in mice, we adhered strictly to the following points in technic.

1. The mice were deprived of food and water for a period of about eighteen hours before weighing and injecting. This was to obviate any error in dosage which might be caused by the weight of the contents of the stomach, intestine and bladder. The loss in this period

of time averaged from 2 to 3 gm. per mouse. The deprivation of fluids also allowed a rapid and fairly uniform rate of absorption of the fluid injected.

2. The injection was made into the subcutaneous tissues of the abdomen, and the skin at the site of the puncture was pinched while the needle was being withdrawn and was so held for at least one-half minute after the withdrawal of the needle. This was done to prevent any of the injected morphin solution from oozing out, as we found that the loss of one drop was sufficient to change the results.

3. The amount of morphin sulphate solution to be injected was made up to 0.4 c.c. This was accomplished by making a 4 per cent. solution of morphin sulphate and diluting the amount of solution required with distilled water to 0.4 c.c. Furthermore, the 0.4 c.c. of morphin solution was injected into two different places, 0.2 c.c. in each, the needle being partly withdrawn after the injection of the first 0.2 c.c. and then reinserted at a different angle for the second injection of 0.2 c.c. We found this method to give us the most uniform rate of absorption. In our early trials we made use of a straight 4 per cent. morphin sulphate solution, making a single injection with the idea that the amount of fluid injected should be in direct proportion to the body weight of the mouse, thereby eliminating the factor of dilution of the blood. However, we soon discovered that the factor of dilution was less important than the factor of uniformity of absorption. In injecting a like total amount of fluid in each mouse regardless of weight, the tension of the confined fluid injected and the area exposed for absorption are the same for every one of the mice of a series. These two factors have a marked bearing on the uniformity of absorption.

4. In order to gain greater accuracy we used a standardized 1 c.c. tuberculin syringe and needles one and one-half inches long, which were inserted their full length before injecting. The morphin sulphate solution was freshly prepared for each experiment. It might be interesting to note in this connection that in determining the depression of the freezing point of a 4 per cent. solution of morphin sulphate, we found it to be hypotonic as compared to a physiologic sodium chlorid solution.

It is unnecessary to tabulate all our results, only those which approximate our minimal fatal dose. Table 1 shows the results of the minimal fatal dose tests.

We took as our end reaction, as to the time of death, only the mice which died within 4 hours. The majority of mice died within this time; the ones surviving had usually recovered from the acute stage of poisoning in so much as they were able to take food. Very

few of the mice in our series died after the four hour period. This we ascribe to causes other than the acute intoxication. Table 2 shows the time of death of the mice enumerated in Table 1.

These two tables show that of animals receiving 0.3 mg. or less of morphin sulphate per gram weight, the majority die. In other words, the minimal fatal dose of morphin sulphate as closely as we can determine it is between 0.3 and 0.4 mg. per gram weight of mouse. Any protective effect of the serum ought, therefore, to be shown definitely with a dose at or about 4 mg. per gram. The proportion of mice surviving this dose should be noticeably greater with the serum than without, if the latter has any immunizing properties whatever.

TABLE 1.—Results of Minimal Fatal Dose Tests

Dose of Morphin SO₄ per Gm. Weight	No. of Mice Tested	No. Mice Dead Within 4 Hours	Per Cent. of Deaths
0.2	20	7	35
0.3	16	5	31
0.4	30	18	60
0.6	10	8	80

TABLE 2.—Time of Death

Time of Death in Hours	Dose of Morphin Sulphate per Gm. Weight of Mouse				
	0.2	0.3	0.4	0.6	Total
0– 1	0	2	0	0	2
1– 2	3	1	10	2	16
2– 3	4	2	7	6	19
3– 4	0	0	1	0	1
4–24	2	0	1	2	5

Having determined the smallest dose of morphin sulphate which is fatal to the majority of mice receiving it, we proceeded to a determination of the protective action of the serum.

In one series of experiments we made use of the serum of a morphin tolerant dog. This animal maintained an approximate weight of 5 kilograms throughout the period of morphinization. He was started on a dose of 10 mg. daily and this dose was gradually increased until at the end of three and one-half months the animal was receiving 80 mg. daily. In the beginning, the 10 mg. produced definite symptoms; at the end of this period the 80 mg. produced none. This final dosage reached in the animal would correspond approximately to a gram per day in the average human which represents the usual amount taken by morphin addicts. When the blood was drawn the dog had received no morphin for a period of eighteen hours.

The technic followed with the mice is the same as described above, with the exception that after weighing the mice, 1 c.c. of the serum was injected into the subcutaneous tissues over the back, and after a period of from three to four hours the required amount of morphin sulphate was injected.

TABLE 3.—RESULTS OF INJECTION OF SERUM AND OF MORPHIN

Mouse	Weight of Mouse in Gm.	Time of Injection of Dog's Serum	Time of Injection of Morphin Sulphate 0.4 Mg. per Gm.	Result
1	25.5	12: 20	4: 04	Died 6: 45
2	26	12: 19	4: 02	Survived
3	26	12: 19½	4: 03	Died 6: 15
4	25.5	12: 20½	3: 58½	Died 6: 10
5	25.5	12: 21	3: 59½	Survived
6	21.5	12: 22½	3: 43	Died 6: 20
7	21.5	12: 22	3: 41½	Died 5: 35
8	21.5	12: 28	3: 44½	Survived
9	21.5	12: 27½	3: 47	Died 6: 00
10	21.5	12: 27	3: 45½	Died 6: 00

This table shows that serum of the morphin tolerant dog did not convey any immunity to the mice.

The analysis of the figures of this series show that 70 per cent. of the mice died within the four hour period, which is slightly more than in the control experiment of mice receiving no serum as shown in Table 1. One must conclude, therefore, that the serum of a morphin tolerant dog does not contain any protective substance against morphin.

In a second series we duplicated the experiments of Series 1, using the serum of a human addict, who had been taking morphin for six years and whose daily doses ranged from 10 to 12 grains of morphin sulphate. A period of three and one-fourth hours elapsed between the last dose of 2½ grains and the drawing of the blood. The patient at this time was very uncomfortable and felt that he was in great need of his morphin.

The serum from this blood was injected into a series of mice in 1 c.c. doses between 5:00 and 5:20 p. m.; the required amount of morphin sulphate was injected the next morning as shown in Table 4. The technic was the same as above stated with the exception as to the time of injection of the serum.

Here again we find a mortality of 70 per cent on a dosage of 0.4 mg. morphin sulphate per gram weight, following an injection of a human addict's serum. These results show that the serum had no protective substance against the morphin. Similar results were obtained with doses of 0.3 mg. of morphin sulphate with the same serum as used above; out of six mice injected, three mice dying and three surviving.

Group 2: Cats.—In this series of experiments we simply attempted to repeat the work of Gioffredi on cats, using, however, the serum of human addicts who were under strict hospital supervision; the blood being drawn as long as possible after the last dose of morphin.

Our technic was as follows: The cats were first weighed, the serum injected into the external jugular vein without any anesthetic, and at varying periods of time the required dose of morphin sulphate was injected subcutaneously.

TABLE 4.—RESULT OF INJECTION OF MORPHIN FOLLOWING INJECTION OF SERUM

Mouse No.	Weight of Mouse in Gm.	Time of Injection 0.4 Gm. Morphin Sulphate	Result
1	24	11: 27½ a.m.	Died 1: 48 p.m.
2	24	11: 29½ a.m.	Died 1: 33 p.m.
3	23	11: 08 a.m.	Died 1: 35 p.m.
4	23	11: 10 a.m.	Died 12: 55 p.m.
5	20	11: 23 a.m.	Died 12: 35 p.m.
6	20.5	11: 21 a.m.	Died 1: 30 p.m.
7	20	11: 37 a.m.	Died 2: 05 p.m.
8	20	11: 33 a.m.	Survived
9	19.5	11: 41 a.m.	Survived
10	22	11: 16 a.m.	Survived

We divided the time for the injection of the serum into four different periods taking the time of the injection of morphin as our starting point: (1) 30 minutes after the morphin injection, (2) simultaneously with the morphin injection; (3) two hours before the morphin injection, and (4) from eighteen to twenty-four hours before the morphin injection. In determining the protective effect of the serum, we took the figures 0.07 and 0.08 gm. of morphin sulphate per kilogram weight of animal given subcutaneously, as the dose which should be survived if the animal were protected by the serum. We used these doses inasmuch as Geoffredi claims that he was able to protect young cats from doses varying from 0.05 to 0.14 gm. of morphin per kilogram given intraperitoneally.

We did not attempt to determine the minimal fatal dose for cats on the same principle as that followed with the mice, because of the difficulty of getting the larger number of cats required, and because Gioffredi's results could be more directly tested by taking a sure fatal dose well within his figures.

Tables 5, 6, 7 and 8 give the results of our experiments.

TABLE 5.—EFFECT OF MORPHIN SULPHATE GIVEN BEFORE THE SERUM

Cat	Weight in Kg.	Dose of Morphin Sulphate per Kg. Gm.	Time of Injection of Morphin Before Serum	Amount Serum	Death
5	2.47	0.08	22 minutes	10 c.c.	2½ hrs.
6	2.23	0.08	33 minutes	10 c.c.	2 hrs.

TABLE 6.—Effect of Morphin Sulphate Mixed with the Serum and Given Subcutaneously *

Cat	Weight in kg.	Dose of Morphin Sulphate per Kg.	Dose of Serum	Death
7	3.0	0.08	10 c.c.	4 hours
8	2.7	0.08	10 c.c.	Survived

* In this experiment we allowed the mixture of morphin sulphate and serum to stand over night before injecting. In the morning we found that the morphin had precipitated out. On mixing morphin sulphate solution with normal human serum in the same proportions, we found that precipitation also occurred. We therefore do not feel that this is a specific effect of addict's serum but due, most likely, to the alkalinity of the blood, or its salts reacing with the morphin.

The survival of cat 8 may be attributed, we think, to the fact that absorption was much delayed by the precipitation of a good part of the morphin salt.

TABLE 7.—Effect of Morphin Sulphate Given a Short Period After the Serum *

Cat	Weight in Kg.	Time Serum Given Before Morphin	Dose Serum	Dose Morphin Sulphate per Kg.	Death
9	3.06	2 hours	10 c.c.	0.07	Over night
10	3.0	1 hour	10 c.c.	0.07	Over night
11	2.43	1 hour	8 c.c.	0.07	2½ hours

* In the cats that died over night, we do not know the exact time of death, as they were injected very late in the afternoon and no observations were made until our return to the laboratory the next morning. In both cases the cats had been dead for a considerable period of time as they were cold and very rigid.

TABLE 8.—Effect of Morphin Given from Eighteen to Twenty-Four Hours After the Serum

Cat	Weight in Kg.	Dose of Serum	Dose Morphin Sulphate per Kg.	Death
2	1.97	10 c.c.	0.08	2 hours
3	1.52	10 c.c.	0.08	4 hours
4	2.13	12 c.c.	0.08	3 hours
12	3.37	10 c.c.	0.07	2½ hours
13	2.76	9 c.c.	0.07	2½ hours
14	2.73	10 c.c.	0.07	1½ hours

SUMMARY

We wish to emphasize the following features of our work:

1. The difficulty attendant in determining a minimal fatal dose of a drug, especially calling attention to the factor of uniformity of absorption of subcutaneous injections.

2. That the minimal fatal dose of morphin sulphate for mice is a question which depends very largely on the technic followed; with our technic it proved to be between 0.3 to 0.4 mg. per gram weight of mouse.

3. The acute stage of morphin intoxication has reached its height within four hours after the subcutaneous injection, and recovery usually occurs if this period is survived.

4. That serum of the blood of a dog tolerant to morphin sulphate does not protect mice against a minimal fatal dose of morphin sulphate.

5. That the serum of the blood of human addicts does not protect mice against a minimal fatal dose of morphin sulphate.

6. That 10 c.c. of serum of humans addicted to morphin did not protect cats from doses of from 0.07 to 0.08 gm. of morphin sulphate per kilogram regardless of the sequence or of the interval of time elapsing between the injection of the serum in relationship to the injection of the morphin sulphate.

7. The morphin tolerance does not develop immunizing properties in the serum either of dogs or of human beings.

<div align="center">DISCUSSION</div>

It will be seen that our work gives results which are in direct conflict with the claims of Gioffredi, Hirschlaff and von Marikovsky, all of whom believed that they had established definite protective substances in the serum of morphin tolerant animals.

In studying the work of Gioffredi, especially as reported in his second paper, we find an absence of tables and protocols, making it impossible to subject his experiments to a critical analysis. His results as stated by him appear convincing, but are not presented in such a form as to permit of intelligent discussions, and amount to little more than statements of conclusions. It may be noted that no attempt has been made in that long period since the publication of his report, to confirm his work by experiments on cats.

Our own experiments (Tables 5, 6, 7 and 8) permit of direct comparison with his stated results, with the difference that he used the serum of a single tolerant dog, whereas we used the serum of a number of tolerant human beings. Except for the possibility that the serum of the dog used by him happened to possess some peculiar quality, not due to the tolerance, it is impossible to reconcile his results with ours.

He states that if the serum is injected within one hour after the morphin it will protect against doses ranging from 0.08 to 0.10 gm. per kilogram; and if within from fifteen minutes to half an hour, against doses ranging from 0.11 to 0.13 gm. per kilogram. If injected simultaneously it would protect against doses up to 0.13 gm. per kilogram.

In the experiments analyzed in tables 5 and 6 we used the lowest of all the doses mentioned, and did not find any protective effect, unless the survival of the one cat mentioned in Table 6 be attributed to causes other than precipitation.

Gioffredi further states that if the serum is given before the morphin, it will protect against doses ranging as high as 0.14 gm. per kilogram, and this even if given as long as from ten to fifteen days before.

Tables 7 and 8 show no protection against doses as small as 0.07 and 0.08 gm. when the serum was given from one hour to twenty-four hours before the morphin.

The work of Hirschlaff does not require extended comment, as Morgenroth, using the same principle, viz., the determination of a *surely* fatal dose, and testing the protective power of serum against such a dose—found that Hirschlaff's results were due principally to poor methods of determining the fatal dose. We feel that Morgenroth's work clearly proves that no credit is to be attached to Hirschlaff's conclusions, but our own preliminary experiments made us doubt the validity of any conclusions to be drawn, either way, on the basis of the principle of determination of the fatal dose employed by both these workers.

We found that the range of individual suceptibility to morphin in mice is so great that a dose surely fatal to all mice would probably be many times the amount required to kill the average mouse, and we therefore, as set forth above, adopted a different principle, viz., the comparison of percentages of fatalities with and without serum under a given dose previously ascertained to be fatal to a majority of mice. This we believe to be a much more delicate method, and one from which reliable conclusions can be drawn.

Our comment on the work of Hirschlaff and Morgenroth may be summarized by saying that the conclusions of the latter are fully sustained by our own work, following what we believe to be a more reliable method, and that Hirschlaff's conclusions are contradicted by the more careful work of Morgenroth as well as by our own.

The work of von Marikovsky on mice was confined to three mice and one control, and hardly permits of any conclusions being drawn. Von Marikovsky also worked with guinea-pigs, but with these animals, as well as with the mice, his conclusions are based merely on the difference of a short period in the time of death between the serum treated animals and the controls. Our own tests with mice have shown that while a few animals die (apparently not from acute morphin poisoning) after the lapse of four hours, the great majority

either die within that time or definitely recover and survive. We, therefore, do not think that valid conclusions can be drawn from slight differences in the time required to kill.

Berri and Belgrano worked entirely with rabbits, and we are not at present in a position to discuss their work with reference to our own. It may be noted, however, that their method of obtaining the serum claimed to have protective effects was by the production of a substance which they classed as an aggressin, and it is doubtful, in view of what is now understood relative to the so-called aggressins, whether their conclusions could be considered tenable.

The researches of other workers who have attacked the problem in different ways may be referred to as having decided significance. Cloetta's experiments, which were carefully performed, show that the immunity conferred by acquired tolerance is lost very rapidly by the animal itself, and this accords with general experience among human addicts, who show marked symptoms of acute poisoning on attempting to take their previously accustomed dose a few days after withdrawal. If the active immunity, as it may be called by analogy, of the tolerant animal, retaining its entire blood volume, disappears within two days, it is scarcely conceivable that passive immunity could be transferred by a comparatively small injection of serum, and would last, as claimed by Gioffredi, for ten or fifteen days, or as claimed by Hirschaff, four weeks.

Again, as demonstrated by the work of von Egmond and by that of Van Dongen, the sensitiveness to morphin of certain centers of the brain persists after the acquisition of a general tolerance, a fact which is not consistent with the possibility of neutralizing substances in the blood serum.

The researches in immunology bearing on the nature and mechanism of serum immunity have in recent years tended to make it constantly more probable that such immunity is produced only by proteins, and that the tolerance established to certain vegetable alkaloids is of a totally different nature.

CONCLUSION

1. We consider that the definite conclusion to be drawn from our work, which, so far as we know, is the only work of this nature directly testing the question of immunity acquired by the human morphin addict, is that no substance is formed in the blood serum of a human being who has acquired a high tolerance to morphin, which is capable of conferring any degree of immunity to the toxic action of morphin on an animal into which it is injected.

2. Likewise we have been able to show that the blood of a tolerant animal does not contain any protective substance against morphin.

An extensive bibliography on the subject of morphin addiction is contained in an article by Du Metz, J. A. M. A. 72:1069 (April 12) 1919.

THE MARGIN OF SAFETY OF INTRAVENOUS DIGITALIS IN CATS *

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The medical profession has become greatly interested in intravenous therapy in recent years, and although no particular evidence of this enthusiasm has been reflected in the treatment of heart disorders, the work of Eggleston,[1] introducing the administration of large single doses of digitalis by mouth, might well lead others to try the effect of similar preparations intravenously. In the past, intravenous cardiac therapy has been essentially limited to preparations of strophanthin, which is generally considered to be a dangerous procedure. With this in mind, an attempt was made to determine whether the introduction into the blood stream of digitalis in its more complete and less potent form would prove to be a safe method for obtaining a therapeutic effect.

The margin of safety has been taken as the difference between the minimum lethal dose (M.L.D.) and the minimum toxic dose (M.T.D.). We introduce the concept of the margin of safety of digitalis preparations because in the practical use of the drug the therapeutic dose is very close to the toxic dose. Therefore, it is of great importance to know how far removed the lethal dose is from the toxic dose, and whether the margin is greater in some preparations than in others. The minimum lethal dose is that dose which is just required to cause standstill of the heart and death when the digitalis preparation is given in interrupted doses over a period of about one hour, similar to the method of Hatcher.[2] In a previous work by one of us[3] it was shown that the toxic and lethal doses are independent of the speed of administration of the drug from a period of fifteen minutes to four hours; and, therefore, in this work the injections were not given at any constant speed, sometimes producing the lethal effect in about one-half hour and sometimes in two hours or more. Some difference of opinion might exist as to the occurrence of the toxic effect. It is generally thought that the appearance of heart block, changing ventricular complexes, and extrasystoles indicate toxicity. The latter is the most common event in cats, and this was generally considered in timing the

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1. Eggleston, C.: Digitalis Dosage, Arch. Int. Med. **16**:1 (July) 1915.

2. Hatcher, R. A., and Brody, J. G.: A Biological Standardization of Drugs, Am. J. Pharmacy **82**:360, 1910.

3. Levine, S. A.: The Action of Strophanthin on the Living Cat's Heart, J. Exper. M. **29**:485, 1919.

toxic dose. This criterion has the added advantage that it is the most important clinical sign of toxicity, for heart block in itself rarely impairs the efficiency of the circulation, while extrasystoles indicate an increased irritability of the ventricles, and when numerous, certainly diminish the effective output of the heart. The minimum toxic dose, therefore, is calculated in these experiments as the smallest dose that is required to produce extraventricular systoles.

METHOD OF PROCEDURE

Cats were used in preference to other laboratory animals because their reaction to digitalis is more like that of the human subject. The cat was etherized, placed on the animal board and the right front leg and left hind leg connected with the electrocardiograph. A canula was inserted in the right saphenous vein and attached by a small rubber tube to a 10 c.c. calibrated pipet which served as a buret. The normal electrocardiogram was taken, and the dose of the preparation to be used was then allowed to flow into the vein. One minute before each dose an electrocardiogram was taken, until a toxic effect was expected, previous experience having shown about where this was to occur. During the two critical periods, the beginning of toxic and lethal effects, the movements of the galvanometer string were watched carefully, and frequent tracings were taken to detect the earliest abnormality.

Various different digitalis preparations were used. The first was an aqueous extract of powdered digitalis (Marion, Virginia leaf) prepared according to Pratt;[4] the second was Squibb's powdered digitalis leaves prepared in the same way; the third was Squibb's tincture of digitalis, and finally, three different digitalis preparations in ampoules for subcutaneous and intramuscular use were tested. The details of the experiments are given in the accompanying table. In three experiments the average margin of safety (M.L.D. — M.T.D.) of intravenous aqueous extract of digitalis (Virginia leaf) was 50 per cent., that is, it required approximately half as much of the drug to produce extraventricular systoles as it did to cause standstill of the heart. An identical figure (50 per cent.) was obtained in the average of three experiments using the aqueous extract of Squibb's digitalis leaves. The average for Squibb's tincture of digitalis (five experiments) was 40 per cent.; for digifolin ampoules (one experiment) 50 per cent.; for digalen ampoules (one experiment) 56 per cent., and for digipuratum ampoules (one experiment) 64 per cent. It is evident that there are individual variations in different cats, both in the suscepti-

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4. West, H. F., and Pratt, J. P.: Clinical Experience with a Standardized Aqueous Extract of Digitalis, J. A. M. A. **74**:1389 (May 15) 1920.

THE MINIMUM LETHAL DOSE AND MAXIMUM TOXIC DOSE OF VARIOUS DIGITALIS PREPARATIONS

Cat Number	Weight in Kilos.	Drug	Speed of Administration	Toxic (M.T.D.) Dose	Lethal (M.L.D.) Dose	Per Cent of M.L.D. that is Toxic	M.T.D. per Kilo.	M.L.D. per Kilo.	Margin of Safety M.L.D. minus M.T.D., per Cent.	M.L.D. per Kilo. in Gm. of Digitalis Leaves	Time for M.L.D.
1	2.2	Aqueous extract of Virginia leaf	0.5 c.c. every 6 min.[1]	0.033 gm.	0.06 gm.	55	0.015 gm.	0.027 gm.	45	0.11	1 hr. 56 min.
2	2.4	Aqueous extract of Virginia leaf	1.0 c.c. every 6 min.	0.035 gm.	0.07 gm.	50	0.015 gm.	0.029 gm.	50	0.13	1 hr. 20 min.
3	3.2	Aqueous extract of Virginia leaf	1.0 c.c. every 6 min.	0.080 gm.	0.065 gm.	46	0.009 gm.	0.020 gm.	54	0.08	1 hr. 14 min.
4	4.2	Aqueous extract of Squibb's leaf	1.5 c.c. every 24 min.[2]	0.113 gm.	0.188 gm.	60	0.027 gm.	0.045 gm.	40	0.11	1 hr. 44 min.
5	2.9	Aqueous extract of Squibb's leaf	0.3 c.c. every 6 min.	0.088 gm.	0.105 gm.	36	0.013 gm.	0.036 gm.	64	0.09	1 hr. 10 min.
6	2.6	Aqueous extract of Squibb's leaf	0.3 c.c. every 6 min.	0.06 gm.	0.113 gm.	53	0.023 gm.	0.042 gm.	47	0.11	1 hr. 25 min.
7	2.1	Squibb's tincture digitalis	0.2 c.c. very 12 min.	0.1 gm. (1 c.c.)	0.22 gm. (2.2 c.c.)	45	0.048 gm. (0.48 c.c.)	0.105 gm. (1.05 c.c.)	55	0.105	2 hr. 1 min.
8	3.2	Squibb's tincture digitalis	0.4 c.c. every 6 min.	0.16 gm. (1.6 c.c.)	0.28 gm. (2.8 c.c.)	58	0.050 gm. (0.5 c.c.)	0.088 gm. (0.88 c.c.)	42	0.088	41 min.
9	3.5	Squibb's tincture digitalis	0.2 c.c. every 6 min.	0.2 gm. (2.0 c.c.)	0.34 gm. (3.4 c.c.)	59	0.057 gm. (0.57 c.c.)	0.097 gm. (0.97 c.c.)	41	0.097	1 hr. 44 min.
10	3.4	Squibb's tincture digitalis	0.35 c.c. every 6 min.	0.28 gm. (2.8 c.c.)	0.385 gm. (3.85 c.c.)	73	0.082 gm. (0.82 c.c.)	0.11 gm. (1.1 c.c.)	27	0.11	1 hr. 3 min.
11	3.2	Squibb's tincture digitalis	0.5 c.c. every 24 min.	0.30 gm. (3.0 c.c.)	0.45 gm. (4.5 c.c.)	67	0.094 gm. (0.94 c.c.)	0.14 gm. (1.4 c.c.)	33	0.14	3 hr. 30 min.
12	2.3	Digifoline ampoules[3]	0.25 c.c. every 6 min.	0.175 gm. (1.75 c.c.)	0.35 gm. (3.5 c.c.)	50	0.076 gm. (0.76 c.c.)	0.152 gm. (1.52 c.c.)	50	....	1 hr. 19 min.
13	3.1	Digalen ampoules[4]	0.25 c.c. every 6 min.	0.83 mg. (0.5 c.c.)	1.88 mg.	44	0.27 mg.	0.61 mg.	56	....	2 hr. 30 min.
14	1.3	Digiparatum ampoules[5]	0.1 c.c. every 6 min.	0.05 gm. (0.5 c.c.)	0.14 gm. (1.4 c.c.)	36	0.038 gm.	0.11 gm.	64	....	....

1. 100 gm. of Virginia leaf gave 24.5 gm. of aqueous extract.   1 c.c. = 0.005 gm. aqueous extract.
2. 100 gm. of Squibb's powdered leaf gave 39.5 gm. of aqueous extract.   1 c.c. of solution = 0.025 gm. aqueous extract.
3. 1 c.c. = 0.1 gm. digitalis leaves; Society of Chemical Industry, Basle, Switzerland.   (Ciba Co., New York).
4. 1 c.c. = 0.3 mg. amorphous digitoxin, Hoffmann, La Roche Chemical Works, N. Y.   (Made in Switzerland).
5. 1 c.c. = 0.1 gm. of digipuratum powder, manufactured by Knoll & Co., Ludwigshafen.   (Merck and Co., N. Y.).

bility to the drug and in the margin of safety, which varied from 27 to 73 per cent. Similar variations are found in the intravenous use of ouabain.[3] Undoubtedly, similar individual variations in susceptibility to digitalis are present in the human and should always be taken into account in practical therapy. The average margin of safety of all the experiments in this study was 48 per cent. This is identical with the result obtained with crystalline strophanthin or ouabain.[3]

The practical consideration that follows from these experiments is that although the various digitalis bodies, when given by mouth, are generally regarded as much safer than intravenous administration of strophanthin, when the entire digitalis glucosids (either the aqueous or alcoholic extracts) are given intravenously, the same risk is encountered as in using strophanthin. In fact, the rapidity with which the drugs act on the heart does not seem to differ very much no matter what preparation is put directly into the circulation. In one experiment, a single lethal dose was given and the toxic effect occurred in two minutes, and standstill in sixteen minutes. Large single doses of strophanthin produce death in from nine to thirty minutes.[3] In two experiments the interval between injections was purposely prolonged to twenty-four minutes to allow the opportunity of determining how soon after an injection the effect appears. It was found that the toxic effect occurred within three minutes after the injection. In experimenting with crystalline strophanthin, an interval of six minutes between injections was found sufficiently long to bring out any changes, that is, waiting from twelve to twenty-four minutes did not alter the results. Practically the same findings were observed using digitalis; i. e., if an effect is to occur at all with interrupted injections it will result within six minutes after the last one.

CONCLUSIONS

1. The average margin of safety (the difference between the minimum lethal dose and the minimum toxic dose) of various digitalis preparations when given intravenously to cats was found to be 48 per cent.

2. The rapidity with which intravenous digitalis acts is similar to strophanthin, and does not differ appreciably no matter what preparation is put into the blood stream.

3. The risk in intravenous digitalis therapy appears from these experiments to be as great as in intravenous strophanthin.

CONCERNING THE DIAGNOSIS AND TREATMENT OF HYPOTHYROIDISM *

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The results of a comparative study of the clinical and laboratory data for determining thyroid deficiency are reported herewith. There is very little difficulty in recognizing the average well-developed case of myxedema or cretinism, but our observations show that cases of mild thyroid deficiency are probably more numerous than has previously been supposed; also that some will remain unrecognized unless special methods are used in diagnosis and control of treatment.

A series of cases of thyroid disease were selected for study. Certain of these cases had been previously diagnosed definitely hypothyroid. Other patients had long been seeking relief from indefinite ill-health previously undiagnosed, which no form of treatment seemed to alleviate. With the exception of one patient, (Case 1940), a child, 2 years old and too young for special methods of examination, the group could definitely be diagnosed by aid of combined laboratory and clinical methods as thyroid deficiency cases. Four individuals in whom symptoms of thyroid deficiency with thyrotoxicosis occurred were regarded as having thyroid dystrophy and were included in these observations.

METHODS OF PROCEDURE

The usual clinical history was written; physical examination, differential blood count, glucose tolerance test, and basal metabolism determinations were made. A study of nitrogen balance was made in two cases, children too young for basal metabolism determinations with the means at hand. The technic of the glucose tolerance tests was that previously developed by one of us,[1] consisting of the ingestion of 1.5 gm. glucose per kilogram body weight in 3 c.c. water per gram of sugar, a sample of blood being withdrawn immediately before the glucose had been taken, and at intervals of one hour, for two or more hours thereafter. The blood sugar was determined by the method of Folin.[2] The basal metabolism determinations were made with the Benedict portable respiration apparatus, following the technic of Francis G. Benedict,[3] in which all patients are required to come to the

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* From the Memorial Metabolism Clinic, Santa Barbara, Calif.
1. Janney, N. W.: J. A. M. A. **70**:1131 (April) 1918.
2. Folin, O., and Wu, H.: J. Biol. Chem. **38**: No. 1 (May) 1919.
3. Benedict, F. G.: Boston M. & S. J. **178**:667 (May) 1918.
4. Barrett, A. M.: Arch. Neurol. & Psychiat. **2**:628, 1919.

laboratory without breakfast and rest at least thirty minutes before the test is begun.   Three readings of ten minutes each were taken in all cases, and the average of the results used as a basis of calculation. Respiratory quotient was assumed to be 0.82.

A brief summary of the cases follows: Data not mentioned may be regarded as normal.   Summaries of the differential blood counts and glucose tolerance tests are given in Tables 1 and 2.

<div align="center">CLINICAL DATA</div>

Included in the present study were members of three thyroid families presenting cases of unusual interest.   Thyroid family 1 proved to have four members suffering from thyroid disease.   This family came under observation because three young children had failed to grow normally.   The remote family history was negative for goiter, obesity, growth anomalies, but always highly neurotic.   The children were reared in the best social environment.

CASE 1 (No. 1938).—Female, aged 6 years (sister of Cases 2 and 3 [Nos. 1939 and 1940]) ; a child of highly neurotic disposition; masturbation at 1 year; growth which was normal until fourth year, but only three pounds had been gained in the last two years.   Few physical abnormalities.   Facial expression normal.   Has eczema and very rough, dry skin.   Perspiration deficient.   Difficultly palpable thyroid.   Slightly protruding abdomen.   Thin, under-developed nails and tendency to decreased muscular tonus.   Metabolic studies show inability to gain weight on large amounts of assimilable food and loss of nitrogen in urine and feces.   The preceding, together with the fact that two other members of the family are quite definitely thyroid cases, and resumption of normal growth, general health and spirits after administration of ¼ grain thyroid extract, seems sufficient proof that the growth anomaly is due to a mild degree of hypothyroidism (Fig. 3).

Diagnosis.—Hypothyroidism; nervous type.

CASE 2 (No. 1939).—Male, aged 5 years (brother of Cases 1 and 3 [Nos. 1938 and 1940]) ; birth weight, 9 pounds and 11 ounces; walked at second year, but not well.   Present weight, 43 pounds.   Talked at twenty-second month. Colitis with bronchitis and asthma in second year.   Tonsils and adenoids removed because of hypertrophy.   Eczema at 1 year.   Otitis media at 3 years. Present height 43 inches.   Cannot reason properly; has defective memory and unreasonable temper.   Has gained 3 pounds during past two years.   Appetite poor.

Physical Examination. — Facial expression not suggestive of cretinism. Patient somewhat thin, hair normal, eyebrows very scanty.   Nose and eyes small; nares flaring.   Skin markedly rough and dry.   Thyroid not palpable. Abdomen definitely protuberant.   Stands with feet wide apart.   Gait slightly waddling, gets up awkwardly and weakly from floor.   Knee jerks normal, no paralysis or atrophy.   Pulse 70, Roentgenologic studies showed marked under-development of base of skull, facial bones and carpi.   Metabolical studies show inability to gain weight on large amounts of assimilable food and loss of nitrogen in urine and feces (Table 4).

Diagnosis. — Hypothyroidism; nervous type.   Improvement on thyroid treatment.

CASE 3 (No. 1940.—Female, aged 2 years (sister of Cases 1 and 2 [Nos. 1938 and 1939], daughter of Case 4 [No. 1936]). Sleeps very poorly. Screams and becomes nervous at the slightest provocation. Birth weight, 9 pounds. Early growth normal. Sept. 8, 1918, weighed 24 pounds 2½ ounces; Jan. 29, 1919, weighed 29 pounds 2½ ounces; Sept. 16, 1919 weighed 30 pounds 6 ounces. Child presents appearance of malnutrition, but no symptoms of cretinism. Physical examination otherwise negative. Certain diagnosis impossible, owing to tender age preventing laboratory tests and control of thyroid treatment. Child probably hypothyroid, in view of family history.

CASE 4 (No. 1936).—Male, aged 55; no complaint. Consulted because of thyroid condition of children (Cases 1, 2 and 3 [Nos. 1938, 1939 and 1940]). No goiter. Has tendency to gain weight of late. Average weight 128 pounds; present weight 135 pounds. Has had noticeable tremor of hands for past two years, following strain of war work. Nervous by nature.

Physical Examination.—Small stature. Manner highly neurotic; body movements very active. Hair of head dry and scanty. Exophthalmos quite marked, but special eye signs negative. Eyebrows, eyelashes, axillary and pubic hair very scanty. Skin normal. Definite fine tremor of extended hands. Panniculus slightly increased. Examination otherwise negative, including thyroid gland. Basal metabolism plus 11 per cent.

Diagnosis.—Thyroid dystrophy.

Thyroid Family 2 has four members, in two of whom hypothyroidism had been diagnosed previously. None of these patients shows typical symptoms, one member, an older brother (aged 17), of Case 6 [No. 1980], presents only a saddle nose and swelling of under lids; otherwise no mental or physical signs of hypothyroidism. His basal metabolism is normal, but he nevertheless tolerates a greater amount of thyroid than does a normal individual. The aunt of this patient shows myxedematous symptoms. Case 6 [No. 1980] proved most interesting, a total deficiency of the outer two-thirds of the eyebrows leading to examination and diagnosis. After three weeks of thyroid treatment, elliptical hyperemic areas developed about the location of the eyebrows which a little later grew to normal proportions. The cases of the mother and this son are as follows:

CASE 5. (No. 1979).—Female, aged 48; divorced; complaining of headaches, feeling of "tenseness," mental dullness, bad memory, loss of power of concentration. Was very stout child. Weighed 130 pounds at 20. Present weight 140 pounds. Menstrual history normal. Three children, one definitely hypothyroid (Case 6 [No. 1980]); another showing hypothyroid symptoms. Always very subject to infections.

Physical Examination.—Flushes easily; tâche cerebralé present. Expression decidedly apathetic. Speech slow. Mentality noticeably sluggish; ready forgetfulness during questioning. At times irritable without provocation. Panniculus largely increased, hands and feet cold, rather short and thick, no padding. Nails frail, skin dry and harsh. Hair of head scanty and dry. Axillary and pubic hair scanty. Eyebrows defective at outer third. Lids drooping, eye signs negative. Legs nearly hairless. Reflexes normal. Thyroid palpable, normal size and texture. Initial basal metabolism, —19 per cent.

Diagnosis.—Hypothyroidism. Improved on thyroid therapy.

CASE 6 (No. 1980).—Male, aged 12; referred by hypothyroid mother (Case 5 [No. 1979]). No complaint. Healthy looking boy. A little dull at school. Skin dry. Pulse 78. Genitals undeveloped. Hands and feet cold, short and stubby; slightly cyanotic. Eyebrows very scanty, outer two thirds absent. Saddle nose. Slight fulness of lower lids. Thyroid scarcely palpable. Panniculus normal. Patient has had uvula amputated because of unusual size. Initial basal metabolism, —26 per cent.

Diagnosis.—Hypothyroidism. Improvement on thyroid therapy.

Thyroid Family 3 presented a number of abnormal individuals, only two of whom could be obtained for clinical study (Cases 7 and 8 [Nos. 1906 and 1907]). All members of this family have a tendency to obesity. One sister, not reported, weighed 225 pounds at 50, then developed exophthalmic goiter; another suffered from dementia praecox and one nephew had periodic insanity. The interesting feature in this family is the presence of degenerated thyroids associated with insanity among its members. This association will be alluded to later in the article.

CASE 7 (No. 1906).—Female, aged 66 (sister Case 8 [No. 1907]); school superintendent. Complaining of obesity, swelling of ankles, slight dyspnea, constipation, exhaustion. Dyspnea very slight, with some palpitation. Menopause at 38, sudden termination.

Physical Examination.—Pulse 56; facies heavy, but is mentally quite alert; obese; hair gray, dry; eyebrows, axillary and pubic hair scanty; skin dry, cool, showing considerable atrophy. Extremities cold. Arcus senilis marked; eye movements normal. Thyroid not palpable. Postcervical fat pad. Systolic murmur at apex; abdomen rotund, large amount of subcutaneous fat. Slight edema of ankles, large fat pads around both ankles, especially on inner surfaces. Basal metabolism, —23 per cent.

Diagnosis.—Hypothyroidism; mitral insufficiency. Definite improvement on thyroid therapy.

CASE 8 (No. 1907).—Female, aged 70 (sister of Case 7 [No. 1906]); widow. History of high blood pressure, complaining of dizziness and obesity. Has gained weight since 45 years of age, from 130 pounds to 196 pounds. Present weight, 174 pounds. Some swelling of ankles for four or five years. Severe headaches before 50. Always very subject to infections.

Physical Examination.—Short, obese. Skin shows senile or endocrinic atrophy, very dry; eyebrows scanty, especially outer third. Thyroid scarcely palpable. Dorsal cervical padding. Heart enlarged. Abdomen relaxed, panniculus greatly increased. Extremities cold, short and stubby. No hair on legs. Definite padding on inner surfaces of both ankles. No edema. Blood pressure, 190/80. Blowing systolic murmur over aortic area; accentuated second pulmonic and aortic sounds. Urine showed faint cloud of albumin; no casts; low specific gravity. Basal metabolism and sugar tolerance could not be studied.

Diagnosis.—Hypothyroidism; chronic diffuse nephritis. Improved under thyroid therapy.

CASE 9 (No. 19104).—Male, aged 56; complains of nervousness, obesity, nervous exhaustion. Was very fat child; weighed 218 pounds at 14; 265 pounds at 17. Mentality keen. Always nervous. "Nervous breakdown" at college with severe melancholia. Second breakdown at 35 years. Became impotent at 35. Declared "thyroid case" at 48, and became potent after three weeks thyroid treatment. Present weight, 205 pounds.

Physical Examination. — Large frame, small bone development. Hair of head dry and scanty. Earlobes fused to head. Brown cutaneous pigmented areas. Subcutaneous tissue firm in areas, soft in others. Skin of back shows patches of roughened epidermis. Eyebrows scanty in outer third; eyelashes very scanty. Slight von Graefe's sign, pupils sluggish to light. Thyroid definitely palpable (small for size of patient). Abdomen obese. Feet show padding on plantar surfaces. Reflexes normal. Initial base metabolism, —20 per cent.

Diagnosis.—Hyperthyroidism. Recovery under thyroid therapy.

CASE 10 (No. 1998).—Female, aged 28; nurse. Headaches, obesity. Very fat child, weighed 120 pounds at 12 years. Present weight, 175 pounds. Height, 4 feet 11 inches. Menstruation irregular, very painful. Always nervous and emotionally unstable; recurring headaches, producing nausea and vomiting.

Physical Examination.—Short, heavy, obese. Stubby hands and feet. Definite fat pads at back of neck, over deltoid and inside of knees. Skin over upper extremities thick, harsh and cold. Hair normal. Thyroid not palpable. Initial basal metabolism, —14 per cent.

Diagnosis.—Hypothyroidism. Headaches immediately relieved by thyroid treatment.

CASE 11 (No. 1960).—Female, aged 40; nurse; exophthalmic goiter at 17. Thyroidectomy with removal of right lobe and isthmus at 31, at which time she was extremely nervous, and had some tremor and exophthalmos. Weight, 130 pounds. Subsequent uncontrollable gain in weight to 160 pounds, with swellings about eyes, mental dulness and lassitude.

Physical Examination.—Pulse slow; panniculus greatly increased; skin cold, harsh in spots; hair dry and coarse; hands and feet thickened; eyes slightly prominent, otherwise normal; nails brittle; typical myxedematous expression; puffiness of lower lids. No thyroid tissue palpable. Reflexes faint but present. Initial basal metabolism, —38 per cent.

Diagnosis.—Cachexia strumipriva. Cured by thyroid therapy.

CASE 12 (No. 1954).—Female aged 45, no vocation; general ill health, dizziness, poor memory and depression. Surgical menopause after oophorectomy eight years ago. Dizziness noticeably increased recently. Swimming sensations when lying down. No really definite complaint.

Physical Examination. — Panniculus greatly increased; enormously over abdomen. Hands cold, nails frail; hair dry and brittle; slight trembling of lids on closing. Flushes easily. Thyroid normal size; slight cutaneous atrophy; reflexes normal; pulse, 72. Initial basal metabolism, —16 per cent.

CASE 13 (No. 1991). — Female, aged 40; complaining of headaches and malaise. General health poor for five or six years. Headaches frontal and left side, sometimes generalized. Subject to infections. Five years ago patient became melancholic, irritable and nervous. Began taking thyroid extract on own initiative. Condition improved. Has taken 1 or 2 grains daily for four or five years. Gained 10 pounds in ten days one year ago while without thyroid. Marked improvement under controlled treatment.

Physical Examination. — Pulse, 60; height, 5 feet 3 inches. Panniculus greatly increased. Hands and feet small and stubby. Bone skeleton heavy for stature. Some cutaneous atrophy at knees and elbows. Skin dry, harsh and scaly. Hair dry. Eyebrows normal; eye signs negative. Tongue soft and small. Definite padding at base of toes and pedal surfaces. Reflexes normal. Initial basal metabolism, —11 per cent.

Diagnosis.—Hypothyroidism. Cured by thyroid therapy.

CASE 14 (No. 19112).—Female, aged 58; no occupation; dragging sensation in abdomen; fits of depression, melancholia. Tendency to gain in weight. Easily upset by trivial household worries. Complete hysterectomy thirty years ago. Mother and brothers had no eyebrows, and hair of body was very scanty.

Physical Examination.—Facial expression mildly myxedematous. Mentally active, but patient very irritable and complains of inability to concentrate thoughts. Panniculus slightly increased. Eyelids tremble slightly on closing. Eyebrows very faintly developed. Earlobes fused to head; slight puffiness of lower lids. Thyroid palpable. Slight padding of supraclavicular fossae. Abdomen relaxed, panniculus greatly increased. Extremities cool, skin very smooth, dry; nails frail and toe-nails quite atrophic. Definite cutaneous atrophy at elbows and lower limbs. Initial basal metabolism, —19 per cent.

Diagnosis.—Hypothyoridism. Improvement on thyroid treatment (see discussion).

Case 15 (No. 19101).—Female, aged 27; complaining of physical exhaustion. Grew normally as child. Growth terminated at 16. Much smaller in stature than other members of her family. Mentality exceptionally keen. Perspires excessively, especially arms. Of lively disposition and quick in movements. Best weight, 112 pounds; present weight, 106 pounds. Height, 5 feet.

Physical Examination. — Pulse, 80, but tachycardia on slight provocation. Patient flushes easily. Hair falling recently. Slight exophthalmos for past three years, with Stellwag sign, but no other special signs. Thyroid slightly increased in size. Palms moist. Tongue large; heavy mouth and lips. Skin normal texture, except for coarse areas over shoulders. Cutaneous pigmentation at elbows, axillary and inguinal folds. Uterus abnormally small. No other signs of hypothyroidism than noted. Basal metabolism, plus 5 per cent.

Diagnosis.—Thyroid dystrophy, tending to thyrotoxicosis.

Case 16 (No. 1964).—Female, aged 37; no occupation; complaining of periodical enlargement of the thyroid and physical exhaustion. Glandular enlargement occurs every three or five days, lasts from three to four days, and disappears. No relation to exercise, mental condition, or menstruation. Patient not markedly nervous nor annoyed by trifles. Psychoneurotic and emotionally unstable. Patient has gained 15 pounds in last year.

Physical Examination.—Does not look her age. Neurotic expression. Eyebrows normal. Eyelids tremble on closing. Corneal reflex dull. No other eye signs. Nares dilated, lips full. Mouth large in proportion to face. Tâche cerebralé present. Flushes easily. Tongue voluminous and fissured. Thyroid, little, if any, increase in size. Abdomen obese. Patient's movements suggestive of myxedema. Extremities cool, skin extremely coarse in places, no hair on hands; skin of thighs coarse; hands short and broadened. Distinct tremor of thyroid type. Thickened subcutaneous tissue. Reflexes normal. Basal metabolism, —14 per cent.

Diagnosis.—Thyroid dystrophy, with hypothyroid tendency. No treatment.

Case 17 (No. 20213).—Female, aged 51; no occupation; complaining of enlargement of neck. Enlargement began six years ago, accompanied by increased pulse rate and slight prominence of eyes. No noticeable tremor or nervousness. No mental disturbance. Subject to tonsillitis in youth. Articular rheumatism and hay-fever in early life. Always over weight, from childhood on. Highest weight, 180 pounds; present weight, 170 pounds. Subject to headaches.

Physical Examination.—Large frame, rather heavy features; hair good condition, eyebrows scanty; flushes and perspires easily (recent development). Suggestion of exophthalmos and Stelwag's sign. Puffiness of lower lids. Temporal veins congested. Breathing stridulent, occasional brassy cough. Slight saddle nose. Tongue large, shows definite tremor. Both lobes of thyroid markedly enlarged; right lobe larger and more dense than left. No fixation. Heart and lungs negative. Abdominal panniculus greatly increased. Hands short and stubby, moist palms, fine tremor. Nails small, frail and brittle. Legs smooth and hairless. Knee jerks slightly exaggerated; other reflexes normal. Hair distribution normal, but axillary and pubic hair very scanty. Basal metabolism, —10 per cent.

Diagnosis.—Thyroid dystrophy. Treatment expectant. Lobectomy advised, if pressure symptoms grow worse.

DIAGNOSIS OF HYPOTHYROIDISM

Relative Importance of Clinical Symptoms.—In seventeen consecutive cases we have encountered but one clearly cut case of cachexia strumipriva presenting the entire classical syndrome of myxedema. All the other cases, with exception of four cases of dysthyroidism, were of the masked type of hypothyroidism originally described by Hertoghe. The strong familial tendency of thyroid disease is illustrated by the finding of three thyroid families among our series.

In order to determine as far as possible with our limited material what points in the ordinary clinical examination are most important in the diagnosis of thyroid deficiency, Table 1 has been prepared, in which the relative frequency of the symptoms is noted. The following may be mentioned as important from the standpoint of occurrence being found in more than 50 per cent. of cases: history of obesity, particularly in early life; mental symptoms, marked liability to contract infections, hair anomalies, dry, harsh skin with pigmentation and atrophy; cold extremities and cold skin generally, decreased size of thyroid, subnormal temperature, pulse and respiration.

TABLE 1.—RELATIVE FREQUENCY OF THYROID SYMPTOMS

	Cases or Per Cent.
Ancestry with history of glandular disturbances or obesity	3 or 17
Personal history of tendency to obesity	12 or 70
Mental symptoms	11 or 64
Including:	
1. Mental dulness	3 or 17
2. Irritability	7 or 41
3. Headache	5 or 29
4. Melancholia	4 or 23
5. Poor memory	3 or 17
Anomalies of development	5 or 29
Liability to infection	9 or 51
Exhaustion or lassitude	6 or 35
Physical signs:	
Hair anomalies	12 or 70
Dry, harsh skin, with pigmentation or atrophy	13 or 76
Frail, poorly developed nails	6 or 35
Cold extremities and skin	9 or 52
Stubbiness of hands and feet	7 or 41
Dull expression, heavy lips, large tongue, saddle-nose	7 or 41
Increased panniculus	12 or 79
Thyroid:	
Enlarged	2 or 11
Normal	4 or 25
Decreased	11 or 68
Fat pads:	
Dorsum of hands, feet, supraclavicular fossa and back	7 or 41
Subnormal temperature, pulse and respiration	14 or 81

With regard to the relative importance of special symptoms, slowing of pulse, respiration and a subnormal temperature seem to have particular significance. These changes were present in 81 per cent. of this series, including very mild cases. They seem at times to represent possibly the only signs of latent thyroid deficiency. For example, Case 199,

not included in the detailed clinical study, may be cited. A lady complained for years of nervous and physical exhaustion on slight provocation. Careful medical review of her case recorded a negative family history, with exception of two sisters having a similar condition and slow pulses. Physical examination, essentially negative, with exception of a slow pulse, 54 minute. The basal metabolism, —11 per cent., was at the lower level of normal, but suggested possible slight hypothyroidism. A trial of 0.4 mg. thyroxin per day, resulted in a few weeks in general improvement. The pulse and the basal metabolism rose to normal. This therapeutic test would seem to justify a diagnosis of latent hypothyroidism in this case.

Examination of the thyroid may be quite misleading. Twenty-five per cent. of our cases exhibited thyroid glands normal to physical examination. It must likewise be remembered that involution of the thyroid takes place as age advances. A small thyroid in an elderly individual is per se no evidence of myxedema, unless the gland be scarcely palpable, which should arouse suspicion. Family history suggestive of thyroid disease, fat padding, marked frailty and brittleness of the nails, growth anomalies, though less frequent, are, when present, of diagnostic importance. Sufficient attention is not always given to examination of the hair and nails, which are very often anomalous in thyroid disease. Dystrophies of hair and nails are nearly always present in myxedema, thus bespeaking their relative importance. In our series their less frequent occurrence may be ascribed in many instances to the mildness of the thyroid deficiency.

Mental symptoms, as a result of latent hypothyroidism, are more common than usually accepted by the neurologist or internist. Very few hypothyroid cases show, if carefully observed, a normal mentality. We look too often for mental lassitude, forgetting that symptoms of mental irritability are also very frequently met with. Sometimes the picture is only that of neurasthenia. It may, however, go on to insanity. In one of our thyroid families, one individual had dementia praecox, another periodic insanity. Such cases may not be on a thyroid basis, but only accompanying degenerative phenomena. Simple failure of memory and the power of concentration are frequently met. A very interesting thyroid family of sixty-two members has recently been reported by Barrett,[4] marked anomalies of the hair and nails being present in many members, together with mental conditions and other signs of degeneration.

The Differential Blood Picture.—The blood in thyroid disease, as first pointed out by Mennacher, tends to revert to the fetal type which is characterized by a preponderance of the lymphocytic elements, with corresponding decrease of the polymorphonuclear cells, together with a mononucleosis. This has been clearly demonstrated by the work of

Kocher and his pupils, Falta,[5] McCarrison,[6] and others. These changes come on early and are very persistent, occurring in both hyperthyroid and hypothyroid cases. It seems strange that previously the diagnostic significance of the differential count in masked hypothyroidism has not been sufficiently emphasized. In all but one case of one series, this blood picture was present (Table 2) the average of thirteen adult patients being: polymorphonuclears, 55.1 per cent.; lymphocytes, 36.1 per cent.; large mononuclears, 3.53 per cent. The mononucleosis is rather constantly present. In children more than the normal lymphocytosis, also mononucleosis, is found. We have not observed eosinophilia, except in one hypothyroid case after thyroid treatment. Eosinophilia has been reported in hyperthyroid cases.

TABLE 2.—Differential Blood Counts in Thyroid Cases *

Case No.	Poly-morpho-nuclears	Lympho-cytes	Large Mo-nonu-clears	Eosino-phils	Other Ele-ments	Remarks
1960	62	33	4	0.3	0.7	Before adequate treatment
	55	38	3	1	3	After treatment
1954	48	45	6.3	0.6	0.1	Before treatment
1906	55	38	4	1	2	Before treatment
19112	61	35	3	1	0	Before treatment
1998	49	49	1	0.3	0.66	Indifferent treatment
1980	65.3	32.3	1.6	0.6	0	Before treatment
1979	49	43	5	0.66	2.33	Some previous treatment
1907	63	32	4	1	0	Before treatment
1938†	42	55	1	1	1	Before treatment
1939†	49	49	1	1	0	Before treatment
19104	55	40	2	1	2	After long unsystematic treatment
1940†	30	67	1	2	0	Before treatment
1936‡	58	35	4.5	2.5	0.0	No treatment; thyroid dystrophy
19101	63	28	6.6	2	0.4	No treatment; thyroid dystrophy
19213	73	21	1	2	3	No treatment; thyroid dystrophy
Average of adult cases	51.1	36.1	3.53	0.99	1.09	

* Three hundred cells counted.
† Not included in average (children).
‡ Two hundred cells counted.

This same type of differential blood count is, unfortunately, not pathognomonic of thyroid conditions, as it is exhibited by various endocrine disturbances, such as Addison's disease and hypopituitarism. It seems possible, however, from the finding of an eosinophilia in a number of hypopituitary cases by Falta and co-workers, that this might prove a differential point in diagnosis from hypothyroidism on further observations in a large series of cases. In cases of uncertain symptomatology, we have found the differential blood count to be very helpful as corroborative evidence, together with the basal metabolism and the blood sugar tolerance curve, in determining the diagnosis of thyroid disease.

5. Falta, W.: Diseases of Ductless Glands, Ed. 2, Philadelphia, 1916.
6. McCarrison, R.: The Thyroid Gland in Health and Disease, New York, William Wood & Co.

THE BASAL METABOLISM

No more interesting example of the successful application of a purely experimental method to modern clinical medicine exists than in the case of basal metabolism. But a few years ago determinations of the basal metabolism were necessarily carried out only in a very few physiologic laboratories, sufficiently well supported to bear the enormous expense of the upkeep of a respiration chamber. The reduction of this method to clinical utility by the recent introduction of smaller apparatus, especially the Benedict portable form, is now being followed by its coming into general use. We are indebted to Plummer [7] for the clinical application of basal metabolic study on a large scale. This method has the immense advantage of being entirely objective, and is thus peculiarly applicable to borderline cases.

In common with Magnus-Levy, DuBois,[8] Means and Aub,[9] we have also found this method the best laboratory aid to diagnosis of thyroid conditions we now possess. It has been applied in every case of the present series. Enthusiastic as we are in its use, attention should be called, however, to certain limitations for avoidance of errors.

The estimation of basal metabolism is a method of precision. Even with the simplest possible technic, the method must be constantly used to insure accuracy. There will be shown on the side of clinicians, perhaps, a too great dependence on this single laboratory procedure, especially when in some cases the technic may be fairly questioned. In using the small Benedict apparatus, only variations in basal metabolic determinations of more than 10 per cent. from the normal can be considered of significance. A moderate increase in basal metabolism above 10 per cent. may be due to other factors, such as fever, faulty determinations due to movement of patient, etc., as well as to hyperthyroidism.

Variations in the metabolic rate are not necessarily due to thyroid disease. Thus we have observed a rate of —15 per cent. in hypopituitarism. Depression of the metabolic rate from 20 to 40 per cent., is usually clearly indicative of thyroid deficiency. However, it must again here be remembered that patients in lowered states of nutrition may show greatly depressed metabolic rates. Thus, among diabetics without thyroid disease, we have observed rates as low as —35 per cent. The metabolic rate may also fail to serve as an exact criterion in early cases of hyperthyroidism, and even exophthalmic goiter,

7. Plummer, H.: Proceedings of the American Medical Association, New Orleans, 1920.

8. DuBois, E. F.: Arch. Int. Med. **17**:915 (June) 1916.

9. Means, J. H., and Aub, J. C.: Arch. Int. Med. **24**:404 (Oct.) 1919.

although in the vast majority of cases, it is a great aid to the appreciation of the severity of the case as well as to therapy. Thus can be quoted a case of exophthalmic goiter recently observed by us showing thyroid hypertrophy, tremor of fingers and tongue, sympathicotonia, moist palms and soles, nervousness and excitability, exophthalmos, Stellwag's sign, the glistening eyeball, rapid pulse on slight provocation, loss of weight and strength, indeed, all the symptoms necessary for a diagnosis, yet the basal metabolism was 5 per cent. below normal. Sound clinical judgment should never be unduly influenced by laboratory methods.

THE BLOOD GLUCOSE TOLERANCE TEST

This test, as applied to the thyroid, is founded on substantial experimental basis [10] which may be cited in abstract. Normal values for the blood sugar and the blood glucose curve were obtained by us in a series of dogs. The thyroid glands were then removed, the presence of intact parathyroids being determined by subsequent postmortem. After complete recovery, the blood sugar level was again observed and blood sugar tolerance curves established. In every case marked hypoglycemia and a remarkably flattened curve resulted with a delayed return of the blood glucose to the normal.[11]

It was therefore expected that a hypoglycemic delayed curve would be found typical for hypothyroidism in the human being, especially as subsequent studies demonstrated marked hypoglycemia in Addison's disease and Frölich's syndrome, as well as in muscular dystrophy, which is probably a hypofunctional endocrinic syndrome.[12] Our present studies, however, make it very doubtful whether a hypoglycemic hypothyroid blood glucose curve, as distinguished from a possible hyperglycemic hyperthyroid curve, can be really established. As is shown in Figure 1, hypoglycemic, hyperglycemic and normal blood sugar curves have been found in our hypothyroid cases. Though hyperglycemic curves may be due in part to thyroid treatment, these differences can scarcely be ascribed to technic, as the quantitative precautions now in general use were adopted.[1] From our experience, we may merely conclude that hypoglycemia and a lowered blood sugar curve are more common in hypothyroidism than in hyperthyroidism. Here we would call attention to a point usually insufficiently emphasized in blood sugar studies. As important at least as the height of the hyperglycemic response to sugar ingestion is the time required after ingestion of glucose for return to the normal blood sugar level. Individuals

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10. Janney, N. W.; Goodhart, S. P., and Isaacson, V. I.: Arch. Int. Med. **21**:188 (Feb.) 1918.

11. Janney, N. W.: Arch. Int. Med. **22**:162 (Aug.) 1918.

12. Janney, N. W., and Isaacson, V. I.: Arch. Int. Med. **22**:160 (Aug.) 1918.

with sound endocrinic organs show remarkable constancy in this regard, if a renal factor be excluded. A return to the normal level may be expected in from one and one-half to two hours from the sugar meal. Thyroid cases in most instances show distinctly delayed curves.
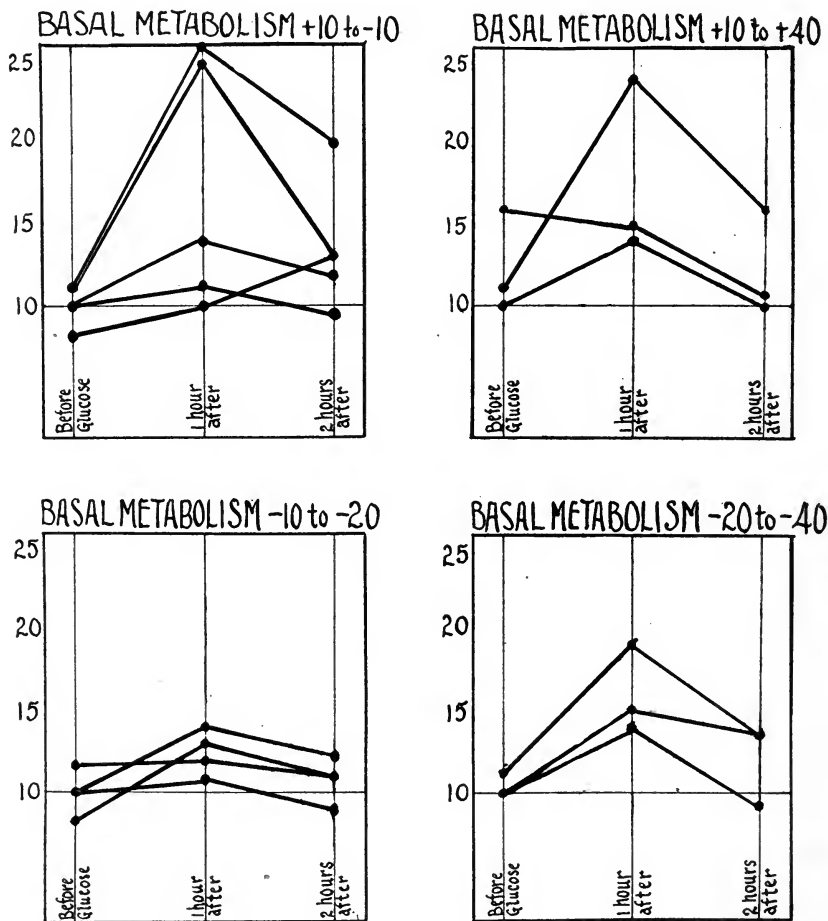
Fig. 1.—Comparison of blood sugar curves to metabolic rate determination in thyroid cases. Cases represented in four groups according to basal metabolic rate. Vertical numbers indicate blood sugar in parts per 10,000. The vertical lines refer to hours.

This, then, seems the one thing characteristic. The experimental recorded evidence quoted above would tend to give added importance to this observation, which has also been reported by Denis,[13] Lueders [14]

13. Denis, W., Aub, J. C., and Minot, A. S.: Arch. Int. Med. **20**: 964 (Dec.) 1917.

14. Leuders, C. H.: Arch. Int. Med. **24**:432 (Oct.) 1919.

and others in describing blood sugar studies. We are, however, confronted with the fact that other endocrinic dystrophies give likewise abnormal glycemic tolerance curves, showing this and all other abnormalities observed in thyroid diseases. One is, therefore, forced to the conclusion that an abnormal blood sugar tolerance curve (whether hyperglycemic, hypoglycemic, or merely a delayed return to normal) is to be regarded solely as a general indication of endocrine disturbance. Inasmuch as the highest curves with glycosuria are observed in exophthalmic goiter, and the lowest curves accompanied by increased sugar tolerance in hypothyroidism, such modifications of the curves are more likely to occur in cases exhibiting respectively hyperfunctional and hypofunctional conditions of the thyroid. Of this, however, there is no certainty in any given case.

In Figure 1 a number of blood sugar curves from various thyroid cases are grouped according to the basal metabolic rate. It will be seen, as also recorded by McCaskey,[15] that there is no definite relationship between either the height or delayed response in these curves, and the metabolic rate. A case of thyroid dystrophy with normal metabolic rate gave a markedly high and delayed curve with glycosuria. A myxedema patient with a —40 per cent. metabolic rate gave a hyperglycemic curve, 10, 16, 13 parts per 10,000 at hourly intervals. In spite of all the foregoing criticism, the blood sugar curve is, however, not without its practical utility in endocrine cases. Instances have already been observed in which the gaseous exchange is normal but evidence of disturbance of metabolism was afforded by the abnormal blood sugar curve. This we have observed in dysthyroidism and in incipient cases of hyperthyroidism. A case of mild exophthalmic goiter exhibited a normal metabolic rate, but the blood sugar curve (8, 17, 13 parts per 10,000 at hourly intervals) showed both increase in height and markedly delayed return to the normal level. An accurate blood sugar curve can often be obtained when elaborate basal metabolic apparatus is not accessible. For these reasons we suggest that blood sugar curves be made in all doubtful cases of endocrinic disturbance in addition to metabolic determinations.

THE NITROGEN METABOLISM

In connection with the present research we have investigated, mainly for the great theoretical interest connected with the same, the nitrogen metabolism in two cases of mild hypothyroidism in children of thyroid Family 1 (see above). The diets employed were of normal mixed constituents and in slight excess of the requirements for

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15. McCaskey, G. W.: J. A. M. A. **73**:243 (July 26) 1919. New York M. J. **110**:607 (Oct.) 1919.

each child at the age when the experiments were undertaken. Both children were retarded in growth, and showed slight clinical signs of hypothyroidism. Proper care was exercised in execution of this work by adopting the same technic as hitherto used in numerous nitrogen balance experiments. The results were striking (Tables 3 and 4). The child presenting the less severe clinical symptoms failed to gain even a gram of nitrogen in a week's time; the other, exhibiting more thyroid deficiency, actually lost nitrogen. Interesting experimental evidence of defective thyroid function was thus afforded.

TABLE 3.—Nitrogen Balance in Hypothyroidism, Case 1 (No. 1938)

| Days | Weight in Kilos | Total Calories | Calories per Kilo | Food Nitrogen Grams | Urine N_2 | Feces | | Nitrogen Balance |
						Grams	Total N_2	
1	25.7	1359.3	67.8	10.1	8.9	....	......	
2	25.0	1709.8	67.8	9.9	12.6	....	......	
3	25.0	1759.5	70.3	10.1	9.16	....	......	
4	25.2	1960.3	77.6	11.0	10.84	....	......	
5	25.4	1966.2	77.8	10.2	9.2	....	......	
6	25.4	1635	64.3	11.8	7.56	....	......	
7	25.4	1750	68.9	11.1	10.84	....	......	
Total	....	......	....	74.2	69.11	95.8	4.48	plus 0.66 gm.
Daily average	....	......	....	10.8	9.88	....	0.63	plus 0.093 gm.

TABLE 4.—Nitrogen Balance in Hypothyroidism, Case 2 (No. 1939)

| Days | Weight in Kilos | Total Calories | Calories per Kilo | Food Nitrogen Grams | Urine N_2 | Feces | | Nitrogen Balance |
						Grams	Total N_2	
1	19.8	1451.2	75.9	8.04	9.7	....	......	
2	19.7	1503.8	75.9	7.8	11.6	....	......	
3	19.9	1523.5	77.3	9.6	12.58	....	......	
4	19.8	1957.3	88.1	9.9	6.25	....	......	
5	19.8	1959.3	91.3	10.1	6.25	....	.....	
6	19.8	1550.7	78.0	10.1	10.5	....	......	
7	19.8	1526.5	77.0	8.1	6.48	....	......	
Total	....	......	....	63.64	63.36	90.8	5.959	—5.95
Daily average	....	......	....	9.09	9.05	....	0.835	—0.195

We have previously made use of the nitrogen balance to demonstrate the synthetic action of the thyroid gland on protoplasm, but did not recommend this as a clinical method for general use. In spite of this, in recent literature our nitrogen balance experiments have been criticized as cumbersome and not to be preferred to the basal metabolism, etc., all of which would, of course, be applicable, had we advanced nitrogen balance experiments as a clinical test in thyroid disease. In the examples just described, however, the nitrogen balance work served a direct clinical aim as the results obtained enabled

us to verify the obscure diagnosis of possible hypothyroidism in children too young for metabolic basal rate determination with the means at hand.

The Therapeutic Test in the Diagnosis of Hypothyroidism.—Although put in the background by the introduction of the laboratory aids to diagnosis, the therapeutic test is not to be forgotten in doubtful cases. Recent exact studies have, however, emphasized that there is a very definite thyroid requirement in each case of thyroid deficiency. If no definite therapeutic effect therefore, be observed, either too little or too much thyroid hormone may have been administered and the thyroid factor remain undiscovered. Full effect only takes place slowly. A trial of several weeks, at least, is usually necessary before judgment can be passed.
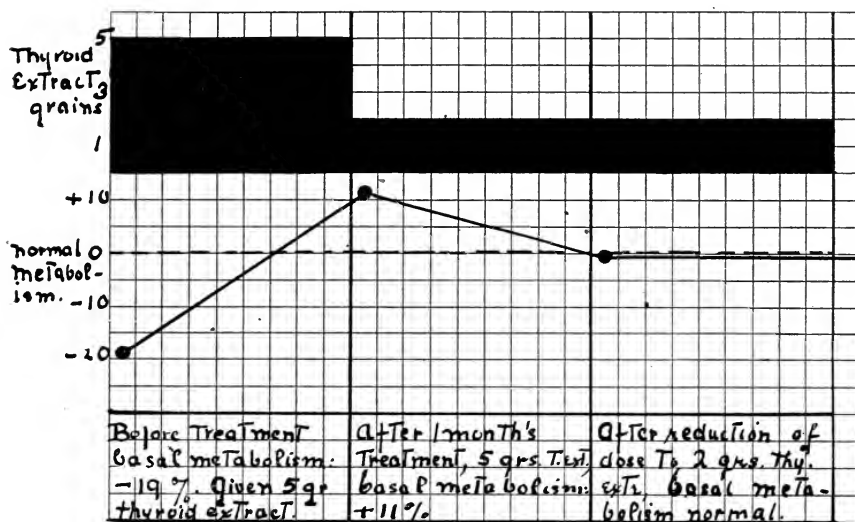
Fig. 2.—Treatment of hypothyroidism controlled by basal metabolism determinations, Case 5 (No. 1979).

TREATMENT OF HYPOTHYROIDISM

It has been our custom for the past year to control the treatment of cases of hypothyroidism by basal metabolism studies. With judicious thyroid treatment, it is surprising with what rapidity the basal metabolic rate rises, accompanied with prompt improvement of all clinical symptoms. In most cases there is excellent parallelism between the clinical course and the basal metabolic rate, as Figures 2 and 3 indicate. Frequently a change in the metabolic rate will give, even before the clinical symptoms, a clear indication for change in dosage. This is, of course, of great advantage in treatment, as the
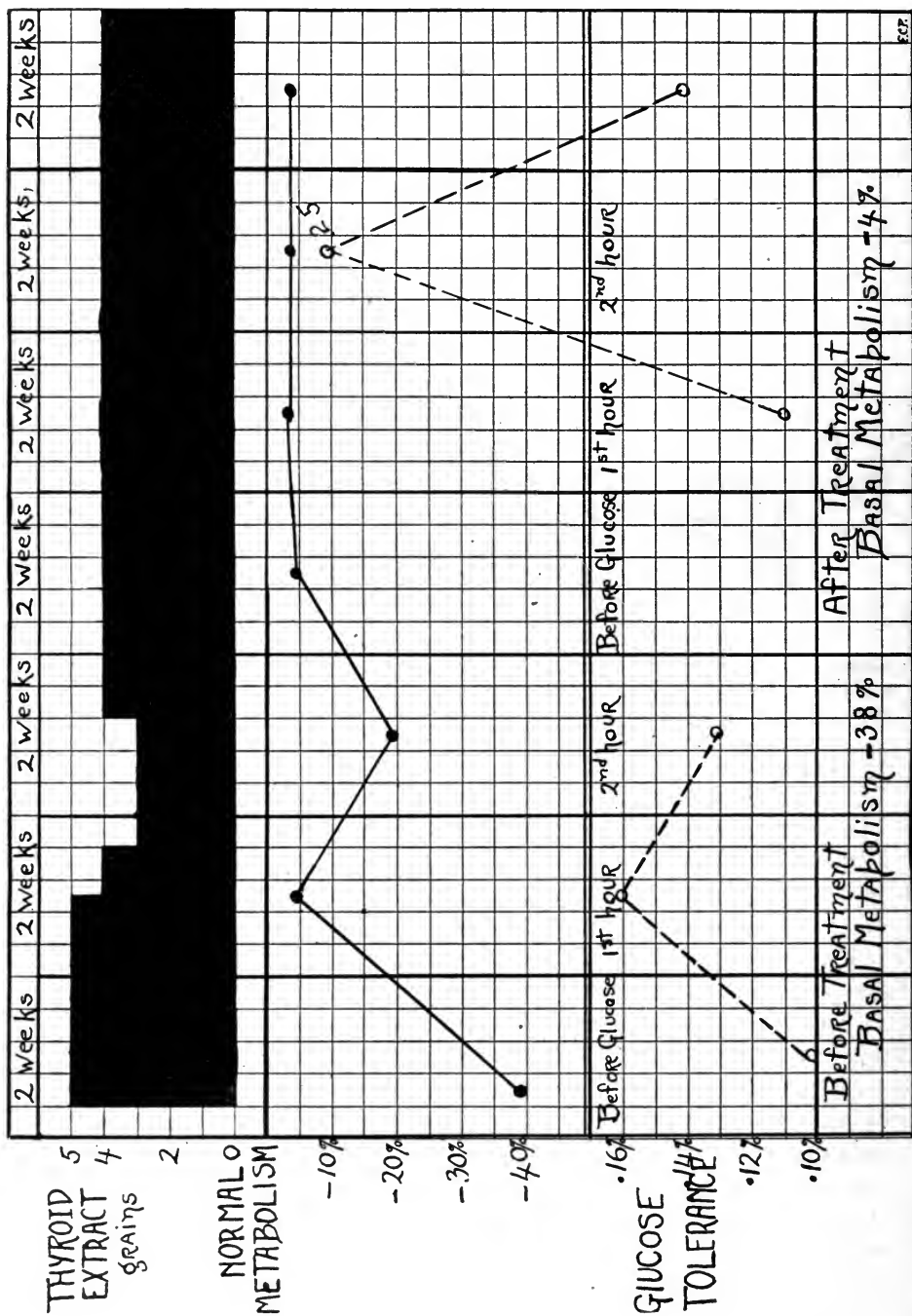
Fig. 3.—Treatment of cachexia strumipriva controlled by basal metabolism determinations, Case 11 (No. 1960).

personal factor of clinical judgment can be balanced by an exact physical method. Frequently, too, necessary variations in dosage can be controlled very accurately by metabolic rate determinations. We fear, however, that there will develop a tendency in the profession to put too great confidence in a normal metabolic rate. We have observed several cases of hypothyroidism in which thyroid caused a permanent return to the normal rate in short order, but clinical improvement, even after months of treatment, was not very satisfactory. The patients remained over weight, mentality was only partly improved, pulse and temperature subnormal. One must, of course, be mindful that the brilliant results of thyroid treatment in young children cannot always be duplicated in adult cases of many years standing, where skeletal and other organic changes must be regarded as permanent. Moreover, maximal improvement may require months or even years.

An interesting and discouraging group of cases in regard to therapy are the dysthyroid cases, previously discussed. In these borderline cases, as evidence accumulates, the basal metabolic rate will probably prove very helpful in indicating proper therapy. There is present a confusing complex of "hyper" and "hypo" symptoms, with basal metabolic rates which may be slightly above, below normal, or exactly at the normal level, due regard being given for the limits of error of the method. These cases showing decreased metabolic rates can properly be regarded as preponderantly hypothyroid and given thyroid treatment with expectancy of some improvement. For those showing normal or slightly increased rates, little can be done. A thyroidectomy would incur the risk of subsequent myxedema. Fortunately many of these cases are nonprogressive, some, indeed, being so little inconvenienced by their symptoms that their medical condition is only accidentally discovered.

Attention is called to two cases of hypothyroidism in women (Cases 12 and 14 [1954 and 19112]) having previously undergone complete removal of ovaries. In these cases the basal metabolism could not be brought to normal, although it improved on thyroid treatment, as symptoms of distress, palpitation and rapid pulse intervened even on small thyroid doses. The question of depression of the basal metabolism through loss of ovarian function is brought up by these findings.

Now that the thyroid hormone has been duly discovered, its chemical formula and characteristics, also physiologic effect, well established by the splendid researches of E. C. Kendall, it is advisable to use this preparation to the exclusion of all others depending more or less uncertainly on their thyroid hormone content. In 1917, Kendall presented us with an amount of thyroxin for metabolism study at the

Montefiore Hospital, New York.   Further experience has been gained during the past year, when it has been in routine use.   In all ways can we corroborate the findings of the Mayo Clinic as to the physiologic and clinical effect of thyroxin.   Already put on a commercial basis, this preparation has the sole objection of being somewhat expensive at present.

GENERAL ASPECTS OF METABOLISM IN HYPOTHYROIDISM

There still remains considerable confusion with regard to modern conceptions of thyroid function.   This, to a great extent, has been due to the antithesis between hypothyroid and the so-called hyperthyroid symptoms, as originally drawn by Kocher.   On this has been built the hyperthyroid theory of exophthalmic goiter which has of late received additional impetus through the extension of basal metabolism determinations to clinical medicine.   The increase in the metabolic rate has been accounted for by a purely dynamic theory of thyroid function. There are, however, many criticisms which render such a theory inadequate.   These have been discussed by various writers, including one of the present in an earlier communication,[16] and are not pertinent to the present paper.

Study of the metabolism of hypothyroidism is, however, a greater aid to a clearer conception of thyroid function than the perplexing picture of thyrotoxicosis.   Since Magnus-Levy's discovery of the decreased metabolic rate exhibited by cretins and myxedematous individuals, little experimental data had been added for a number of years.   A reinvestigation of this subject was therefore undertaken in 1915 by one of us (N. W. J.) and his co-workers.   This has been continued recently in our Santa Barbara Clinic, and additional data are included in the present report.

Since the decreased basal metabolic rate of cretins was accounted for by Magnus-Levy and others, as being caused by defective food absorption due primarily to alimentary tract sluggishness, exact feeding experiments [12] were undertaken which demonstrated that absorption of food from the intestines of athyroid animals was just as active as in normal animals.   This led to further work on cretins, bringing out the fact that thyroid deficient patients failed to absorb as much nutritive material from the intestinal tract as normals, not because the alimentary function was necessarily deficient, but because such subthyroid individuals could not utilize digestive products in the normal manner, whether for fuel, tissue repair, or replacement purposes, *after* this food was assimilated by the intestinal tract.   As was clearly demonstrated in prolonged metabolic experiments, when thyroid extract or thyroxin was administered in proper doses to these cretins, there

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16. Arch. Int. Med. **22**:187 (Aug.) 1918.

ensued increased intestinal absorption accompanied by and probably required by increased ability to retain nutritive substances in the body and build them into new tissue. These data were obtained by following the nitrogen metabolism. With the demonstration that large amounts, even 100 per cent. more than previously, of nitrogen were retained on proper thyroid dosage, good, if indirect, evidence was secured that the thyroid synthetically controls the growth, probably also the constructive repair and replacement of tissue. The anabolic function of the thyroid gland on metabolism was thus experimentally demonstrated. Hitherto the thyroid was supposed to exert its effect on metabolism solely through the stimulation of catabolic processes as shown by increased nitrogen loss following the ingestion of thyroid
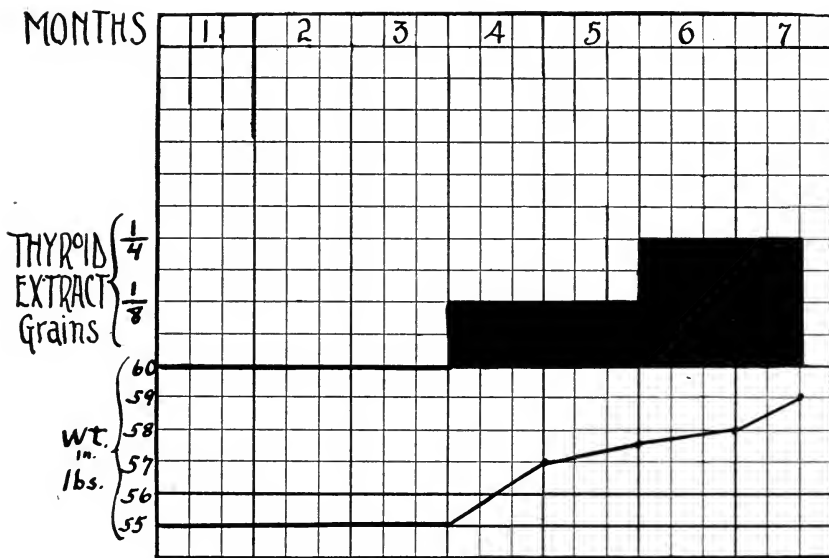
Fig. 4.—Resumption of growth in latent hypothyroidism of childhood with thyroid treatment, Case 1 (No. 1938).

material. Further experiments were therefore carried out demonstrating that the loss of nitrogen in this latter instance is a toxic loss, due to overgreat thyroid dosage.

The two nitrogen balance experiments reported in this paper are further illustrations of the inability of young hypothyroid individuals to properly utilize their food for fuel and growth, this inability being promptly recovered through thyroid treatment, as shown in the growth chart, Figure 4.

At first sight it seems difficult to correlate the well known catabolic action of the thyroid on metabolism with its synthetic function. Increased oxygen consumption and carbon dioxid output are generally

regarded as accompanying phenomena of combustion, i. e., catabolic processes.   Therefore the thyroid has been looked upon as "the bellows which fans the fires of metabolism," and the basal metabolic rate as an exact guide to this function, as recently emphasized by Plummer's clinical studies.   In the interpretation of basal metabolism studies, it must, however, be borne in mind that, in such, merely the total requirement for oxygen and the carbon-dioxid production of the body at a given time are so measured.   *Oxygen, however, is required, as shown in recent intermediary metabolic studies, in anabolic as well as in combustive or catabolic processes.*[17]   Though increase in the metabolic rate is at present the most exact laboratory aid in the determining of thyroid function, this method merely measures the degree of utilization or production of two essentially end products of metabolism. Mere reflection makes it indeed self-evident that, coincident with the establishment of an increased metabolic rate exhibited by a thyroid-fed cretin, true growth must of very necessity be taking place as characterized by the building of new tissue.   Anabolic and catabolic processes are thus occurring coincidentally.   Indeed, it is likely that the anabolic must be in the ascendant or the catabolic would lead to a persistent decrease in body weight of the cretin, which only takes place so far as is determined by the freeing of the organism of myxedematous tissue and fat.

Modern intermediary metabolic studies require, then, the acceptance of the coincident interaction of anabolic and catabolic processes.   Prevalent evidence goes to indicate that the thyroid plays as yet a not clearly definite rôle in the intricate mosaic of these opposed sets of reactions, the end result of this function being the growth and replacement of tissue.   It is probable that catabolism of ingested food products takes place for two reasons; one, to meet the fuel requirements of the organism; two, to supply intermediary split products for synthetic purposes.   It is evident, from experiments showing the effects of ingested food on the thyroid gland of the fed animal, that the thyroid exert an influence in these preliminary catabolic reactions.   Synthetic processes are, however, also carried out by aid of the hormones, of which the thyroid and pituitary are the most important, as is shown by clinical observations of the effect of these glands on growth and development.   It would then undoubtedly render the whole conception of thyroid function vastly more lucid, were we to accept that the thyroid controls those metabolic processes necessary for the satisfaction of the heat, energy and regenerative requirements of the organism, including formation of new tissue.

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17. Dakin, H. D.: Oxidations and Reductions in the Animal Body, New York, Longmans, Greene & Co.

The failure of parallelism between blood glucose determinations in thyroid patients and their basal metabolism (see above) is another indication that the metabolic disturbance in thyroid disease is more complicated than the metabolic rate alone would indicate. There is abundant evidence that the carbohydrate metabolism is abnormal in thyroid disease. There are also much data indicative that carbohydrate intermediary products are actually utilized in protein synthesis. The evidence supporting this view has been collected by Janney [18] and need not be quoted here.

Thus it may be mentioned, only for example, that respiratory quotient studies make it seem unlikely that the great disappearance of carbohydrate in active muscle is merely combustive. Furthermore, it is likely that side by side are two distinct processes taking place; one a degenerative, characterized by carbon dioxid output; another, regenerative, characterized by absorption of oxygen. In view of the anabolic action of the thyroid, as demonstrated by our metabolic experiments, and the close relationship of the thyroid to carbohydrate metabolism, it seems reasonable to draw the inference that the thyroid probably exerts, at least in part, its synthetic action on protoplasm by aid of the products of carbohydrate metabolism. This seems reasonable as it is now known that various amino-acids can be produced in vivo by the aminization of intermediate products derivable from glucose.

These views of thyroid function may now be applied to form a clearer conception of hypothyroidism. In this deficiency disease growth is inhibited; development is arrested; pathologic studies show extensive degenerative processes of the tissues; less food is absorbed from the alimentary tract, and what is absorbed, poorly utilized synthetically as well as combustively, as shown by the nitrogen metabolism studies; carbohydrate metabolism is abnormal; decreased excretion of the purin bodies and the appearance of urinary creatin takes place; metabolic activity is generally lessened, as shown by depressed basal metabolism. The entire picture of hypothyroidism is that of *impairment of tissue growth, regeneration and consequent degeneration* due to hormone hunger. It may, indeed, be possible that the great depression of basal metabolism observed in creatinism is partly, at least, of compensatory nature, energy being spared and all metabolic processes being inhibited on account of the inability to adequately utilize fuel and replacement materials. That such an explanation may apply seems likely from the results of basal metabolism determinations in inanition, in which the rates are quite as low as those of the most marked cases of hypothyroidism which have been recorded. All of these varying factors can be understood and correlated with the aid of acceptance of the view

18. Janney, N. W.: New York M. J. **107**:24 (May 4); 879 (May 11) 1918.

that the thyroid gland controls the metabolic processes, anabolic and catabolic, necessary for the required replacement and repair of the organism's cells, together with the production of heat and energy.

Thyroid therapy leads to stimulation of appetite, as more food can be assimilated for fuel and tissue construction purposes, increased absorption from alimentary tract, the increased combustion and synthetic utilization of the digestive products, as shown by the rise in basal metabolism and the increase in normal elimination of the purins, as their proper replacement and synthesis in the body is now possible; disappearance of creatin, as a sign of cessation of abnormal tissue breakdown. Regeneration thus takes the place of degeneration of tissues, growth and development return to normal.

SUMMARY AND CONCLUSIONS

Latent hypothyroidism is more frequent than generally supposed, as among eighteen consecutive thyroid cases, it was present in twelve, four cases being dysthyroidism and only one presenting classical myxedematous symptoms. Analysis of clinical data shows the following to be present in more than 50 per cent. of our series: history of obesity, particularly in early life, mental symptoms, marked liability to contract infections, hair anomalies, dry, harsh skin with pigmentation and atrophy, cold extremities and cold skin generally, obesity, decreased size of thyroid, subnormal temperature, pulse and respiration. Of all this data, lowered temperature, pulse and respiration occur most frequently, being found in 81 per cent. of our cases. Frequently but few symptoms may be present, diagnosis being impossible without laboratory methods. In the case of children with obscure symptoms, parents should be examined. Attention is called to the diagnostic value of lymphocytosis and mononucleosis in obscure thyroid cases.

The basal metabolic rate is of great value in diagnosis and treatment of hypothyroidism, but cannot be considered an absolute criterion.

The blood glucose tolerance test is abnormal in respect to the height of the curve and delayed return to normal level in the majority of cases of thyroid disease, but is only diagnostic of endocrine disease in general. There is no constant relation demonstrable between the blood sugar curve and the metabolic rate in thyroid disease. The blood glucose curve is, however, of confirmatory value in diagnosis of obscure thyroid cases.

Estimation of the nitrogen balance in two cases of obscure hypothyroidism showed an inability to retain nitrogen, this being further evidence of the synthetic function of the thyroid gland, as further developed in the theoretical consideration.

Treatment of hypothyroidism is best carried out with Kendall's thyroxin and controlled by estimation of the basal metabolic rate.

THE EFFECT OF ETHER ANESTHESIA ON THE ALKALI RESERVE *

AN EXPERIMENTAL STUDY

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The alkali reserve can best be determined by measuring the capacity of the blood for combining with carbon dioxid. Many of the observations to determine the influence of anesthesia on the alkali reserve have been made on patients after surgical operations. The alkali reserve may be decreased by the restricted diet or fasting preparatory to surgical operations, and the same condition is usually present in surgical shock, so that ether anesthesia produced experimentally in animals offers the advantage of eliminating these contributing factors.

Caldwell and Cleveland [1] studied the influence of different kinds of anesthesia on the alkali reserve in more than 100 patients, including fifty-five for whom ether anesthesia was used. In those latter cases they found a slight decrease, varying from 4.5 to 7.7 volumes per cent. in the combining capacity for carbon dioxid, but acidosis approaching dangerous proportions was noted only in the case of a diabetic patient who had acidosis before the operation.

Austin and Jonas [2] determined the carbon dioxid combining capacity of blood in sixteen patients after ether anesthesia for various surgical operations. The maximal decrease was 10 volumes per cent. and the lowest amount observed was 47 volumes per cent. The reduction seemed proportionate to the duration of the anesthesia and was maximal at the close of the anesthesia. When a decrease occurred, it apparently persisted with little alteration for about five hours.

Cannon [3] made a number of observations on soldiers who had been wounded in battle and were suffering from varying degrees of shock. In a series of nine cases of moderately severe shock, there was a decrease of approximately 12 volumes per cent. on the average, the maximal reduction being 16 volumes per cent. He found the decrease occurred rapidly when the capacity of the blood for combining with carbon dioxid was low (below 50 volumes per cent.) before the

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1. Surg., Gynec. & Obst. **25**:22, 1917.
2. Am. J. M. Sc. **153**:81, 1917.
3. J. A. M. A. **70**:531 (Feb. 23) 1918.

operation. The maximal decrease following operations when nitrous oxid and oxygen were used for anesthesia was 8 or 9 volumes per cent. Cannon expressed the opinion that the alkali reserve is below normal in shock, and that the reduction is in direct proportion to the degree of shock.

W. H. Morris [4] made a number of observations on patients before and after gynecologic operations. He also made a few experiments on dogs with prolonged ether anesthesia but without any surgical operation which could produce shock. He found that a reduction of the carbon dioxid combining capacity of the blood usually but not invariably occurs and that it does not bear any relation to the duration of the anesthesia. In one case in which the anesthesia only lasted twenty minutes, there was a decrease of 10 volumes per cent.; in another case lasting two hours for a hysterectomy, the decrease was 7.7 volumes per cent. The greatest decrease was 22 volumes per cent., while the least was 0.4 volumes per cent., and in the latter the operation lasted one and a half hours.

Comparing a series of ten patients to whom from 15 to 20 gm. of bicarbonate of sodium had been given intravenously before operation, with the same number who had not received such preliminary treatment, he found the decrease in the carbon dioxid combining capacity of the blood averaged 5.7 volumes per cent. as compared with an average of 9 in those who had not been given sodium bicarbonate.

He etherized two dogs for two hours or more, making carbon dioxid determinations every half hour. He found a reduction of from 10 to 12.5 volumes per cent., that is, from 22 to 24 per cent. of the normal amount. In one dog, the greatest reduction occurred in the third half hour; in the other the most rapid fall took place during the first half hour. Prolonged chloroform anesthesia in one dog caused a reduction of 24 volumes per cent., or 47 per cent. of the normal amount, which was considerably greater than that caused by ether.

Yandell Henderson [5] investigated the subject by experiments on dogs and reached the conclusion that the reduction in the carbon dioxid combining capacity of the blood is due to increased dissociation of the carbon dioxid from the blood, caused by the hyperpnea or increased respiratory activity produced by the irritant ether vapor. He contends that the decrease in the carbon dioxid content and capacity of the blood is due to increased ventilation of the lungs and not to actual reduction in the alkali reserve of the body.

Previous observations had been made by the Van Slyke apparatus with the plasma alone. Henderson used the whole blood and deter-

4. J. A. M. A. **68**:1391 (May 12) 1917.
5. J. Biol. Chem. **33**:345 (Feb.) 1918.

mined by means of his own apparatus the carbon dioxid content as well as its combining capacity when exposed to an atmosphere containing a uniform amount (5.5 per cent.) of carbon dioxid. He found the maximal decrease in the carbon dioxid content during ether anesesthia was from 14 to 19 volumes per cent., while the greatest decrease in the carbon dioxid combining capacity was from 12 to 15 volumes per cent.

A state of hyperpnea was maintained by artificial respiration in dogs narcotized by chlorbutanol and he states that this produces as great a reduction in the carbon dioxid content and capacity of the blood as that seen in ether anesthesia, although the chlorbutanol alone does not produce that effect. He produced the opposite condition of decreased ventilation of the lungs by morphinizing dogs so as to reduce the respiratory activity, and he found an increase in the carbon dioxid content and capacity of the blood. When he produced light anesthesia with ether, so as to cause an acceleration of the respiration, he found a decrease in the carbon dioxid content and capacity of the blood; when he produced deep ether narcosis with feeble respiratory activity he found that both were increased.

In another series of experiments dogs inhaled ether vapor in an atmosphere containing from 6 to 7 per cent. of carbon dioxid, to which oxygen was added, and Henderson found there was no decrease in the carbon dioxid content or capacity of the blood, although the anesthesia was continued from three to five hours.

This last series of experiments is open to the criticism that the animals were compelled to breathe an artificial atmosphere containing a higher percentage of carbon dioxid than that of the alveolar air. Under such abnormal circumstances it is not surprising that there was an increase in the carbon dioxid of the blood.

EXPERIMENTS

Series 1.—The first series of experiments was made with blood plasma obtained by Van Slyke's method. The jugular vein was exposed after the animal became unconscious at the beginning of ether anesthesia and the first sample of blood was taken as the normal. Other samples were taken after half an hour, one hour, or one and a half hours of anesthesia and the carbon dioxid determinations were made with Van Slyke's apparatus.

Uniform anesthesia was maintained throughout each experiment by causing the animal to breathe ether vapor from a Mason jar of one liter capacity with an adjustable inlet tube and a respiratory valve in the top of the jar (Fig. 1), so that the vapor from the jar entered the cone with each inspiration, while the expired air escaped into the open without entering the jar. The jar was kept in a wooden box, the air of which was warmed by one or two eight-candle power

electric lamps, so that the air containing ether vapor was warmed before it entered the lungs.

The results are shown in Table 1. Only one out of twelve dogs did not show any decrease in the carbon dioxid combining capacity of the blood. Eleven showed a decrease varying from 5.6 to 23.3 volumes per cent., or from 15 to 46 per cent. of the normal. The average decrease at the end of the anesthesia was 10.8 volumes per
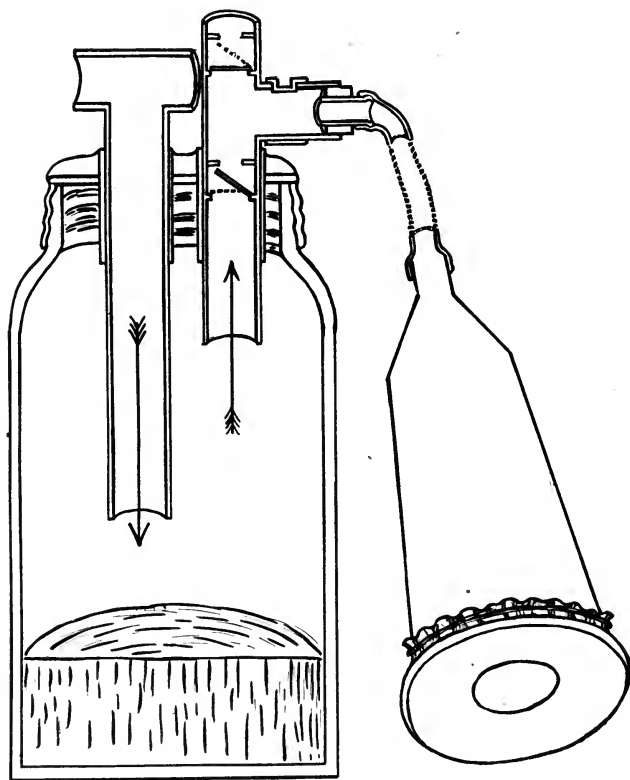
Fig. 1.—Sectional view of ether jar with respiratory valve on top. The continuous lines show the position of the light aluminum disks of the respiratory valve during inspiration, while the broken lines show the position of these disks during the phase of expiration.

cent. The anesthesia lasted one hour in three experiments and one and a half hours in nine experiments. Very little decrease occurred during the first half hour; the greatest decrease occurred during the second half hour, with a further fall during the third half hour period.

The same dog was used in Experiments 4, 5 and 6 on three consecutive days. There was no fall on the third day although there was a decrease on each of the first two days.

The same dog was used in Experiments 7, 8 and 9. The fall was no greater in Experiment 9, although a condition of shock was produced during the last two periods of that experiment by exposing and handling the abdominal viscera, so that the mean blood pressure was reduced from 140 mm. to less than 100 mm., and kept at that level.

One dog was also used for Experiments 11 and 12. This animal showed the greatest reduction in the alkali reserve on the first day, but less on the second day.

TABLE 1.—Summary of the First Series of Experiments. Ordinary Ether Anesthesia. Uniform Ether Vapor Inspired from Ether Jar. Expired Air Escaped Into the Open Without Entering the Jar. Carbon Dioxid Determined by Van Slyke's Method

Experi-ment	Dog's Weight and Date of Experiment	Normal Carbon Dioxid Capacity of Blood	After ½ Hour of Anes-thesia	After 1 Hour of Anes-thesia	After 1½ Hours of Anes-thesia	Decrease in Volume per Cent. (1-1½ Hrs.)	Decrease in Per-centage of Normal
1	10.5 kg.	54.3	....	36.0	....	18.3	33.7
2	13 kg.	51.9	....	....	39.9	12.0	23.1
3	9.5 kg. Aug. 20.......	59.7	50.4	46.7	....	13.0	21.8
4	Same dog Aug. 22...	44.0	....	37.4	37.4	6.6	15.0
5	Same dog Aug. 23...	41.2	....	33.8	33.8	7.4	17.9
6	Same dog Aug. 24...	39.3	....	39.3	....	0.0	0.0
7	13 kg. Aug. 27, 10 a.m.	35.7	....	33.9	30.1	5.6	15.7
8	Same dog Aug. 27, 3 p.m.	33.9	....	26.4	24.6	9.3	27.4
9	Same dog Aug. 28...	42.1	43.0	41.2	34.7	7.4	17.5
10	7.7 kg.	52.05	42.2	37.5	39.3	12.7	24.4
11	5.0 kg. Sept. 5.......	49.7	43.2	31.05	26.4	23.3	46.8
12	Same dog Sept. 7....	59.9	54.3	54.3	46.1	13.8	23.0
	Average..........	46.98	46.6	37.95	34.7	10.8	22.1

Series 2.—In the second series of experiments, the normal blood was obtained before the anesthetic was started, by injecting procain and exposing the jugular vein without causing pain or struggling by the animal. Duplicate determinations were made from the normal blood to avoid error and these are given as the first and second normals.

In this series, and in all subsequent experiments throughout this investigation, the whole blood was used for determining the carbon dioxid content and the carbon dioxid combining capacity of the blood by Yandell Henderson's method and his apparatus was used in all experiments after the first series. The results by this method are more uniform and there is less danger of error than there is by Van Slyke's method.

The ether vapor was inhaled from a Mason jar of 1 liter capacity with the respiration valve in the top as in the first series. Anesthesia was maintained for two hours. Determinations of the carbon dioxid content and carbon dioxid combining capacity of the blood were made at the end of one and two hours of anesthesia, respectively, and also half an hour and one hour after the end of the anesthesia, to determine the after-effect.

The details of these experiments are not given for each separate experiment but they may be summarized by giving the averages of the different periods in the five experiments of this series (Table 2).

All of the experiments of this series showed a decrease, varying from 4.0 to 8.6 volumes per cent. in the carbon dioxid combining capacity of the blood. The results were quite uniform and did not show as much variation as in the first series.

One important fact brought out by this series is that there was practically no decrease in the alkali reserve at the end of one hour of etherization, but the entire reduction occurred during the second hour. This has a practical bearing as it shows that the danger of decrease in the alkali reserve is greater from prolonged anesthesia than it is when this is not continued for more than an hour.

TABLE 2.—SUMMARY OF FIVE EXPERIMENTS. ORDINARY ETHER ANESTHESIA. CARBON DETERMINATIONS BY HENDERSON'S METHOD

Periods for Which Averages Are Given in Last Two Columns	Average Carbon Dioxid Content of Blood	Average Carbon Dioxid Combining Capacity of Blood
First normal (blood obtained by procain)	48.27	48.77
Second normal (blood obtained by procain)	48.04	49.02
After 1 hour of ordinary ether anesthesia	48.45	48.28
After 2 hours of ordinary ether anesthesia	42.86	42.71
One-half hour after end of anesthesia	42.70	43.28
One hour after end of anesthesia	47.09	46.79
Average decrease in volume per cent.	5.38	6.09
Average decrease in percentage of normal	.....	12.5

The reduction in the carbon dioxid content and combining capacity of the blood continued for half an hour after the end of anesthesia in each experiment but both had practically returned to the normal at the end of one hour.

Series 3.—A third series of experiments was made to determine whether there is an actual reduction in the alkali reserve from ether anesthesia, or if this is an apparent condition caused by the hyperpnea or increased respiratory activity as a result of the irritant effects of ether vapor, as claimed by Henderson. The normal blood was obtained from the vein after it had been exposed by the use of procain. The animal was first etherized in the ordinary way until tracheotomy could be performed and etherization was then continued by connecting the tracheal tube to a metal tube in the top of a 2-quart Mason jar containing ether. A large rubber tube from the Hans Meyer artificial respiration apparatus was connected to another tube in the top of the ether jar. This apparatus can be adjusted to force through the ether jar and into the lungs the same amount of air that is breathed in natural respiration by animals of different size. The tidal air had been determined by means of a spirometer for each animal before

the experiment started, and the artificial respiration apparatus was adjusted to furnish the same amount. It also aspirates from the jar and lungs in expiration the same volume of air that is forced in under positive pressure during inspiration. Of course the air in the jar, 2 liters, was added to the dead air space of the upper respiratory passages and analysis of this air in each experiment showed that it contained on the average from 2.6 to 3.0 per cent. of carbon dioxid. The animals used in the third series were, therefore, furnished with ether in a uniform vapor density, in an atmosphere containing approximately 3 per cent. of carbon dioxid. This accounts for the increase in the carbon dioxid content and combining capacity of the blood which occurred after one hour of anesthesia maintained in this way. The increased carbon dioxid of the air would tend to keep up the carbon dioxid of the blood, even if there were a condition of hyperpnea. Hyperpnea was prevented in this series by the artificial respiration which maintained a uniform respiratory rate and volume throughout the entire experiment.

TABLE 3.—SUMMARY OF THREE EXPERIMENTS OF SERIES III. EFFECT OF ETHER ANESTHESIA BY ARTIFICIAL RESPIRATION TO MAINTAIN A UNIFORM RESPIRATORY RATE AND VOLUME, THUS ELIMINATING HYPERPNEA

Periods for Which Averages Are Given	Carbon Dioxid Content of Blood	Carbon Dioxid Combining Capacity of Blood
First normal (blood obtained by use of procain)	51.82	54.18
Second normal (blood obtained by use of procain)	51.95	53.02
After one hour of anesthesia by artificial respiration through a two liter jar containing 2.6-3.0 per cent. carbon dioxid..	53.62	56.15
After two hours of anesthesia	46.06	50.06
After three hours of anesthesia	42.12	44.75
Average decrease in volume per cent. after two hours etherization	5.82	3.54
Average decrease in volume per cent. after three hours etherization	9.76	8.85
Maximal decrease in percentage of the normal amount	18%	16.5%

The elimination of hyperpnea in the experiments of the third series shows that this condition is not responsible for the reduction in the alkali reserve in the experiments of the first and second series where ordinary ether anesthesia was used. In spite of the increased percentage of carbon dioxid in the tidal and stationary or alveolar air, which in itself caused an increase in the carbon dioxid content and combining capacity of the blood during the first hour of anesthesia, there was a decided fall during the second hour and a further fall during the third hour. The fall during the second hour was less than that in the second series, but when the increase during the first hour is taken into consideration, the results are practically the same in both series. The reduction for three hours of anesthesia by artificial respiration is greater than that in the second series and almost as great as the average of the experiments in the first series.

The details of each experiment are not given on account of limited space. The results were quite uniform in the three experiments and these are summarized in Table 3 by giving the averages for the different periods.

Series 4.—This series of experiments was made to determine whether the ventilation of the lungs is increased in proportion to the acceleration of the respiratory rate during ordinary anesthesia; also to devise a method of overcoming the reduction in the carbon dioxid content and capacity of the blood that might be produced by a simple hyperpnea, or increased in the volume of air moved in and out of the lungs, occurring with natural respiration.

The experiments were divided into four periods of half an hour each. The respiratory volume, as measured by a spirometer, and the rate were taken for two or three minutes and averaged for one minute periods. At least six observations were made in each period at intervals of from three to five minutes and the average was taken for the entire period of half an hour.

During the first period the animal breathed through the cone and Mason jar with the respiration valve in the top, but without ether in the jar. The expired air escaping from the top of the respiration valve was collected and measured in a spirometer. This period was taken as the normal for comparison with the other periods.

During the second period the dog breathed through a jar with a respiration valve on the far side from the animal (Fig. 2). In this way the inspired and expired air passed through the jar, the contents of which became part of the dead air space of the cone and upper respiratory passages. Analysis of the air of the jar showed that it contained from 16 to 17 per cent. of oxygen and from 2.5 to 3.0 per cent. of carbon dioxid. Jars of different size (1, 2 and 3 liters) were used, but the composition of the air did not vary much. When such jars are used for vaporizing ether the large size (3 liters) is desirable as the vapor density of the ether does not then exceed the amount desirable for anesthesia.

The third period was like the first, except that ether was placed in the jar for ordinary ether anesthesia.

The fourth period was like the second, except that ether, in sufficient amount to keep the bottom covered, was placed in the jar through which the inspired and expired air passed, so that the animal inhaled ether vapor in an atmosphere containing from 16 to 17 per cent. of oxygen and from 2.5 to 3 per cent. of carbon dioxid.

Six experiments were made in this series and the averages for the different periods are given in Table 4, together with the percentage for each period over the normal. It will be seen that an atmosphere containing from 2.5 to 3 per cent. of carbon dioxid (Period B)

increased the respiratory volume 74 per cent., but only increased the rate 7 per cent. The greater depth of the respirations is caused by the chemical stimulation of the respiratory center produced by the increased tension of carbon dioxid in the blood.

Ether vapor alone in the ordinary atmosphere (Period C) increased the respiratory rate 107 per cent., but only increased the respiratory volume 33 per cent. This indicates that the acceleration of the respiratory rate in ordinary ether anesthesia is three times greater than the increase in the ventilation of the lungs, and that the hyperpnea is not so great as it appears to be when the number of shallow respirations alone are considered.
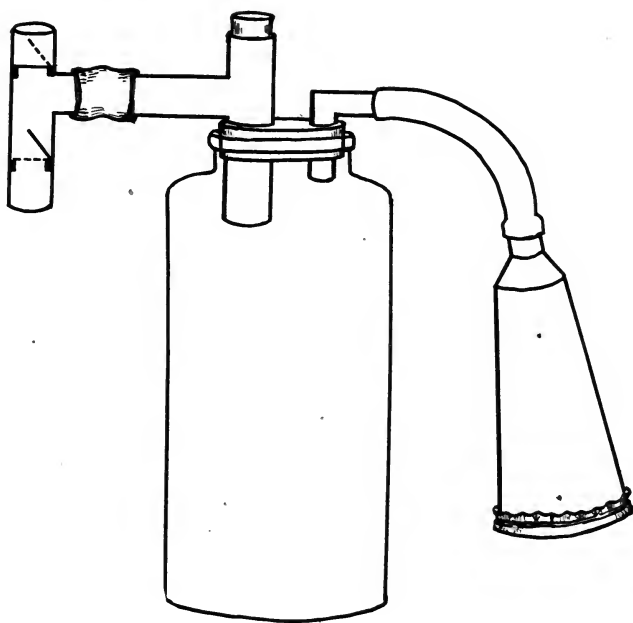
Fig. 2.—Ether jar with respiratory valve on the far side from the cone. The continuous lines show the position of the disks of the valve during inspiration, while the broken lines show the position during expiration.

The average for the fourth period (Period D) showed that the ether vapor in an atmosphere containing 3 per cent. of carbon dioxid caused an increase of 80 per cent. in the rate but the volume is increased less than 5 per cent. The latter varies with the depth of anesthesia, but the increase in the volume is never as great as with ether alone, or an atmosphere of 3 per cent. of carbon dioxid alone. Apparently the depression of the respiratory center by the ether lessens its irritability to chemical stimulation by an increased tension of carbon dioxid

in the blood. The method used in this last period makes it possible to study the effect of etherization on the alkali reserve with natural respiration when there is comparatively little increase in the ventilation of the lungs. Any increase in the volume of air is fully offset by the increased percentage of carbon dioxid in the alveolar air. This was shown by the increased amount of carbon dioxid in the blood which was found in numerous experiments.

TABLE 4.—Summary of Six Experiments to Determine the Effect of (1) Ordinary Ether Anesthesia on Respiratory Rate and Volume; (2) Breathing Through a Jar Containing 16-17% Oxygen and 2.5-3% Carbon Dioxid; (3) Ether Vapor in a Jar Containing 2.5-3% Carbon Dioxid. Six Observations Made for Each Period At Intervals of Three to Five Minutes

Half-hour Periods for Which Averages Were Made	Average Respiratory Rate per Minute	Percentage Increase Over Normal	Average Respiratory Volume (Cubic Inches per Minute)	Percentage Increase Over Normal
A. Normal respiration through Mason jar with respiration valve in top, i. e., breathing ordinary atmosphere........	26	...	109	
B. Breathing through jar with respiration valve on far side. "Dead air space" in jar contained 16-17% oxygen and 2.5-3.0% carbon dioxid..................	28	7	190	74
C. Ether anesthesia. Uniform ether vapor from jar with valve in top, i. e., expired air escaped without entering jar	54	107	145	33
D. Ether anesthesia through jar with valve on far side, i. e., ether vapor in air containing 16-17% oxygen and 2.5-3.0% carbon dioxid	47	80.7	113	3.7

It was not practicable to make simultaneous observations of the respiratory rate and volume and of the carbon dioxid of the blood in many experiments, but the following experiment shows no decrease in the carbon dioxid combining capacity of the blood during one and one half hours of ordinary ether anesthesia, although there was considerable hyperpnea. During the second period of one and one-half hours in the same animal, when the animal inhaled ether vapor in air containing from 3 to 3.5 per cent. of carbon dioxid, there was a decided decrease in the alkali reserve of the blood, although the respiratory volume was practically the same as it had been during the first period.

Series 5.—The experiments of this series were made to determine the effect on the carbon dioxid content and combining capacity of the blood produced (1) by natural respiration through a 3 liter jar containing approximately 3 per cent. of carbon dioxid, and (2) by inhaling ether vapor from such a jar for two or three hours. Observations were also made one and one-half hours after the end of the anesthesia

when it was found that the alkali reserve of the blood had practically returned to normal.

Six experiments were made in this series which are summarized in Table 6 by giving the averages for each period. The dogs breathed through a 3 liter bottle with the respiratory valve on the distal side from the animal and described in discussing results in Period D of Series 4. The air of the bottle was vitiated by respiration so that it contained from 16 to 17 per cent. of oxygen and 3 per cent. of carbon dioxid. The bottom of the bottle was kept covered with ether.

TABLE 5.—EXPERIMENT 12. SHOWING SIMULTANEOUS OBSERVATIONS ON RESPIRATORY RATE AND VOLUME AND CARBON DIOXID CONTENT AND CAPACITY OF THE BLOOD (A) DURING ORDINARY ETHER ANESTHESIA AND (B) DURING ETHER ANESTHESIA WHILE BREATHING 3.5% CARBON DIOXID

	Respiratory Volume (Cubic Inches per Minute)	Respiratory Rate per Minute	Carbon Dioxid Content of Blood	Combining Capacity of Blood
9:30 a. m. First normal (blood taken by procain)	...	...	55.72	5⁻.30
Second normal	...	...	53.80	58.⁻0
Average	...	...	54.76	58.00
9:40–9:50 Average of 4 observations	90	31		
10.00 Started ether anesthesia				
10:00–10:25 Average of 8 observations	186	41		
10:30	...	...	50.90	60.70
10:55–11:25 Average of 7 observations	212	54		
11:30 After 1½ hours of ordinary ether anesthesia	...	...	59.20	63.00
11:32 Began inhalation of ether vapor with 3.5% carbon dioxid by breathing through a 3 liter jar				
11:40–11:55 Average of 4 observations	242	83		
12:00 m.	...	...	46.70	49.94
12:45–12:55 Average of 3 observations	210	86		
1:00 p. m. After 3 hours of anesthesia, i. e., 1½ hours with ordinary air and 1½ hours of ether vapor with 3–3.5 carbon dioxid	...	...	45.92	47.94
Decrease	...	...	8.84	10.06

In the experiments of Series 3, artificial respiration was used through a 2 liter ether jar; in those of Series 5, natural respiration was used through a 3 liter ether jar. In both series the jar contained approximately 3 per cent. of carbon dioxid. Hyperpnea was completely eliminated in Series 3, but not in Series 5. Even if there were any hyperpnea in Series 5, it did not cause any increased dissociation of carbon dioxid from the blood on account of the increased percentage of carbon dioxid in the tidal and in the alveolar air. This is clearly shown by the increase in the carbon dioxid content and combining capacity of the blood when the animal breathed through the jar for half an hour before the anesthetic was started. The animals breathed

quietly during this time and did not struggle. Under such conditions any decrease in the carbon dioxid combining capacity of the blood that occurred in the six experiments of Series 5 could not have been due to hyperpnea.

The reduction was practically the same as that in Series 2, in which the animals inhaled ether vapor in the ordinary atmosphere, and it was three-fourths as great (6.4 volumes per cent.) as that in Series 3 (8.85 volumes per cent.).

TABLE 6.—SERIES 5. SUMMARY OF SIX EXPERIMENTS WITH NATURAL RESPIRATION. ETHER VAPORIZED IN A THREE-LITER JAR CONTAINING 3 PER CENT CARBON DIOXID

Periods for Which Averages Are Given in Last Two Columns	Average Carbon Dioxid Content of Blood	Average Carbon Dioxid Combining Capacity of the Blood
First normal (vein exposed by procain)........................	52.1	52.3
Second normal	53.2	54.1
After breathing through 3 liter bottle containing 3% carbon dioxid (without ether) for one-half hour....................	56.3	57.6
After one hour of etherization (ether vaporized in jar containing 3% carbon dioxid through which the animal breathed)	54.6	54.6
After two hours of anesthesia (6 experiments).................	48.5	49.4
After three hours of anesthesia (3 experiments)...............	46.1	45.4
Average decrease in volumes per cent.	6.16	6.4
Average decrease in percentage of the normal amount..........	11.1%	11.6%
One and one-half hours after end of anesthesia (4 exper.)......	52.7	52.1

As an atmosphere containing 3 per cent. of carbon dioxid causes a distinct increase of 3 or 4 volumes per cent. in the carbon dioxid content and combining capacity of the blood, this method seems much better than the one used by Henderson, in which the animals breathed an atmosphere containing 6 or 7 per cent. of carbon dioxid with the addition of oxygen.

That hyperpnea is not a factor in the decrease in the alkali reserve produced by ether anesthesia is also evident from the fact that the decrease does not occur during the first hour of anesthesia, when the greatest acceleration of the respiratory rate occurs, but during the second or third hour when the respirations are uniform in rate. It is also evident from the six experiments of Series 4 that the increase in respiratory volume is only about one-third as great as the increase in rate in the hyperpnea which occurs early in ether anesthesia.

THE EFFECT OF DECREASED OXYGEN

It is a well known fact that a decreased supply of oxygen to the tissues may produce a decrease in the alkali reserve. In order to determine whether the decrease in the oxygen in the 3 liter jar, through which the animal breathed in order to increase the carbon

dioxid of the tidal and alveolar air, was responsible for the decrease in the carbon dioxid combining capacity of the blood during ether anesthesia by this method, three control experiments were made.

The dogs were kept quiet by giving chlorbutanol to produce narcosis after the normal sample of blood had been taken by exposing the vein with the use of procain. They were then made to breathe through the jar of 3 liters capacity for three hours and the carbon dioxid content and capacity of the blood were determined as before. Analysis of the air in the jar showed an average of 16.3 per cent. oxygen and 3.9 per cent. carbon dioxid. The averages of the three experiments are shown in Table 7.

TABLE 7.—Effect of Decreased Oxygen

	Carbon Dioxid Content	Carbon Dioxid Combining Capacity
Normal blood	58.5	62.6
After one-half hour of chlorbutanol narcosis....................	48.7	55.7
After breathing through 3 liter jar for 1 hour...................	59.2	60.0
After breathing through 3 liter jar for 2 hours.................	57.0	58.4
After breathing through 3 liter jar for 3 hours.................	60.1	58.6

These experiments show conclusively that the decrease in the oxygen in the air breathed from the jar was not responsible for the decrease in the alkali reserve of the blood. The chlorbutanol narcosis seemed to cause a distinct decrease until the respiratory center was stimulated by the increased tension of carbon dioxid in the blood which resulted from a higher percentage of carbon dioxid in the alveolar air. Henderson states that chlorbutanol does not influence the carbon dioxid combining capacity of the blood. However, it lessens the respiratory activity decidedly.

AFTER-EFFECT OF ETHER ANESTHESIA

All five of the experiments of the second series showed that the reduction in the alkali reserve at the end of etherization for two hours continued for half an hour after the anesthesia ended, but the carbon dioxid content and capacity returned almost to the normal at the end of one hour after the anesthesia.

Four of the experiments in Series 5 showed that the carbon dioxid content and capacity of the blood had returned to the normal one and a half hours after the termination of the anesthesia, which lasted for two hours in two experiments, and for three hours in two experiments.

Two other experiments were made to determine if there is a secondary fall. There was an average reduction of 8.5 volumes per cent. in the carbon dioxid combining capacity at the end of two hours

of ordinary anesthesia and this continued for one hour. At the end of two and one half hours the alkali reserve had returned to normal and remained so at the end of four and five hours, respectively, after the anesthesia.

CONCLUSIONS

1. Ordinary ether anesthesia, without any of the contributing conditions that attend surgical operations, causes a distinct decrease in the alkali reserve. The decrease in carbon dioxid combining capacity of the blood of dogs is usually from 6 to 10 volumes per cent.

2. There is comparatively little diminution during the first hour but it occurs almost entirely after that time and is in direct proportion to the duration of the anesthetic.

3. There is an actual decrease in the alkali reserve and not an apparent condition due to hyperpnea. The latter is most marked early in the anesthesia but there is little or no dealkalization during the first hour. The usual decrease occurs when anesthesia is maintained by artificial respiration which provides a uniform respiratory volume; also when an animal breathes an atmosphere containing 3 per cent. of carbon dioxid in which ether has been vaporized.

4. Breathing an atmosphere containing 16 per cent. of oxygen and 3.5 per cent. of carbon dioxid for three hours does not diminish the alkali reserve.

5. The greatest decrease in the alkali reserve produced by ether anesthesia occurs at the end of the anesthesia and remains at that level for from one-half to one hour after the anesthesia, at a time when there is decreased respiratory activity. Following this brief after-effect, there is a rapid increase in the alkali reserve and it returns to the normal in from one to two hours after the anesthesia.

All of the experiments presented in this paper were performed on normal dogs. The decrease in the alkali reserve never reached a dangerous level and it only continued for a short time after the anesthesia. It is impossible to conclude from them what might occur if there is a reduction from altered metabolism before a surgical operation, or when a patient is in a condition of surgical shock which is attended by a reduction in the carbon dioxid combining capacity of the blood. Such conditions, added to that produced by ether, may be more serious. It should also be remembered that it is extremely difficult to produce in dogs the condition known as acidosis, even by injecting large amounts of a mineral acid into the circulation, as they are able to protect themselves against acids by the alkali reserve of the body and by the ability to form ammonia salts from protein metabolism.

STUDIES ON BLOOD SUGAR—EFFECT OF BLOOD CONSTITUENTS ON PICRATE SOLUTIONS

A CONSIDERATION OF THE LIMITATIONS OF THE MODIFIED LEWIS-BENEDICT TEST *

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While working on a blood sugar problem we became interested in the statement of McLean[1] that "it is doubtful whether the picric acid method is at all reliable in the case of whole blood on account of the creatinin (and probably other interfering substances)" which under the conditions of the estimation gives a color similar to that produced by glucose in the presence of picric acid. De Wesselow[2] claims to show that the Benedict method with whole blood gives 45 per cent. higher readings than the McLean method which utilizes an entirely different principle—precipitation of protein with heat and dialyzed iron and a procedure which is thought to overcome the tendency to oxidation of cuprous oxid during titration.

We have done so much work with the Lewis-Benedict method, and it has been so satisfactory in our hands as a clinical test, that we decided to satisfy ourselves as to the correctness of these statements before giving it up as the routine method in the clinic.

The results of our investigation may be of interest. We have done the following experiments which may have some bearing on the reliability of the Lewis-Benedict test and which may give some added information concerning substances which appear in the blood under abnormal conditions that may influence blood sugar records and explain the occurrence of "hyperglycemia" without glycosuria.

The Effect of Oxalation.—Blood was drawn from four diabetics and one normal person. As quickly as the blood was drawn, 2 c.c. were placed in a volumetric flask, laked with distilled water and precipitated in the ordinary way with picrate solution. The blood was not oxalated. The analysis was carried through immediately. The remainder of the blood was oxalated and determinations were made by the Lewis-Benedict method one half hour later (Table 1).

1. Maclean, H.: On the Estimation of Sugar in Blood, Biochem. Jr. **13**:135, 1919.

2. De Wesselow, C. L. V.: Picric Acid Method for Estimation of Sugar in the Blood and Comparison of This Method with that of Maclean, Biochem. Jr. **13**:148, 1919.

· This shows that oxalation produces no difference in the reaction.

The Effect of Creatinin.—We have shown by a simple gross experiment that creatinin added directly to a 2 c.c. sample of blood increases the blood sugar record given by the Lewis-Benedict method (Table 2).

These amounts of creatinin are many times greater than, probably, ever occur in blood in disease. The highest blood creatinin we find recorded is 33.3 mg. per cent. in a case of nephritis due to mercurial poisoning reported by Meyers and Killian.[3]

We next attempted to determine the lowest limit of sensitivity of the picrate solution to creatinin in water solutions and in blood (Tables 3 and 4).

TABLE 1.—Experiment 1. Nov. 12, 1919

Case	Nonoxalated Sample	Oxalated Sample
Labar	0.204	0.200
Cassel	0.175	0.170
Germain	0.200	0.200
Fregel	0.312	0.312
Kozolowski (control)	0.117	0.120

TABLE 2.—Experiment 2. Nov. 22, 1919

Control Blood 0.125%	2 c.c. Blood + 1 mg. Creatinin = 50 mg. per 100 0.180%	2 c.c. Blood + 2 mg. Creatinin = 100 mg. per 100 0.260%

In Series 2 of this experiment a distinct color change with a 2 c.c. sample of a creatinin solution containing 2.5 mg. in 100 c.c. of water is shown. In other words, the picrate solution is sensitive to 0.00005 gm. creatinin in water.

A distinct color change occurs in the picrate solution when 2 c.c. of a solution of 6 or 7 mg. of creatinin to 100 c.c. of water are added to a 2 c.c. sample of normal blood (Table 5). In other words, in order that creatinin in the blood may have any influence on a Lewis-Benedict blood sugar record, it must be increased at least 6 or 7 mg. above normal which would give a creatinin value of 9 mg. per cent. or above.

The remarkable sensitiveness of the picrate solution is better comprehended when we recognize the fact that in the 2 c.c. sample of blood, plus the creatinin solution, there is only 0.00016 gm. of creatinin present.

3. Meyers, V. C., and Killian, J. A.: Prognostic Value of Creatinin of the Blood in Nephritis, Am. J. M. Sc. **157**:674, 1919.

We have seen that the highest blood creatinin is 33.3 mg. per cent.[3] If the record obtained by this amount (0.045, Table 5) added to blood is added to a normal blood sugar record, $0.150 + 0.45 = 0.195$, the upper border of normal is certainly reached. If, on the other hand, a case of diabetes was complicated by a marked renal disturbance inducing a high blood creatinin, one might expect a considerable increase in the blood sugar record not due to glucose.

TABLE 3.—EXPERIMENT 3. DEC. 29, 1919. CREATININ IN WATER. SERIES 1

Size of Water Sample	Creatinin		Blood Sugar Record, L.-B. Test
	Amount Added	Strength of Solution	
2 c.c. control	.....	....	0.040
2 c.c.	2 c.c.	200 mg. in 100 c.c. water	0.333
2 c.c.	2 c.c.	190 mg. in 100 c.c. water	0.285
2 c.c.	2 c.c.	180 mg. in 100 c.c. water	0.270
2 c.c.	2 c.c.	170 mg. in 100 c.c. water	0.270
2 c.c.	2 c.c.	160 mg. in 100 c.c. water	0.270
2 c.c.	2 c.c.	150 mg. in 100 c.c. water	0.250
2 c.c.	2 c.c.	140 mg. in 100 c.c. water	0.250
2 c.c.	2 c.c.	130 mg. in 100 c.c. water	0.222
2 c.c.	2 c.c.	120 mg. in 100 c.c. water	0.225
2 c.c.	2 c.c.	110 mg. in 100 c.c. water	0.222
2 c.c.	2 c.c.	100 mg. in 100 c.c. water	0.222
2 c.c.	2 c.c.	90 mg. in 100 c.c. water	0.215
2 c.c.	2 c.c.	80 mg. in 100 c.c. water	0.220
2 c.c.	2 c.c.	70 mg. in 100 c.c. water	0.220
2 c.c.	2 c.c.	60 mg. in 100 c.c. water	0.182
2 c.c.	2 c.c.	50 mg. in 100 c.c. water	0.166
2 c.c.	2 c.c.	40 mg. in 100 c.c. water	0.143
2 c.c.	2 c.c.	30 mg. in 100 c.c. water	0.135
2 c.c.	2 c.c.	20 mg. in 100 c.c. water	0.090
2 c.c.	2 c.c.	10 mg. in 100 c.c. water	0.090
2 c.c. control	.....	....	0.040

TABLE 4.—EXPERIMENT 3. DEC. 29, 1919. CREATININ IN WATER. SERIES 2

Size of Water Sample	Creatinin		Blood Sugar Record, L.-B. Test
	Amount Added	Strength of Solution	
2 c.c. control	.....	....	0.040
2 c.c.	2 c.c.	60 mg. in 100 c.c. water	0.200
2 c.c.	2 c.c.	50 mg. in 100 c.c. water	0.160
2 c.c.	2 c.c.	40 mg. in 100 c.c. water	0.133
2 c.c.	2 c.c.	30 mg. in 100 c.c. water	0.111
2 c.c.	2 c.c.	20 mg. in 100 c.c. water	0.080
2 c.c.	2 c.c.	10 mg. in 100 c.c. water	0.070
2 c.c.	2 c.c.	5 mg. in 100 c.c. water	0.060
2 c.c.	2 c.c.	2½ mg. in 100 c.c. water	0.050
2 c.c. control	.....	....	0.040

The Effect of Urea.—If 4 or 5 mg. urea crystals are added to a 2 c.c. sample of blood, a color change in the picrate solution may be obtained. This amount is far above the amount that ever occurs in the circulating blood. With graded and accurately measured amounts of urea, such as might occur as excess in circulating blood, no change in color whatsoever takes place (Tables 6 and 7).

Dilutions of urea in blood exactly like those tabulated for water were set up and run. There was absolutely no change produced by these amounts of urea.

TABLE 5.—Experiment 4. Jan. 2, 1920. Creatinin in Blood. Series 1

Size of Blood Sample	Creatinin		Blood Sugar Record, L.-B. Test	Difference from Control Average
	Amount Added	Strength of Solution		
2 c.c.*	.....	....	0.118	
2 c.c.	2 c.c.	190 mg. in 100 c.c. water	0.475	0.356
2 c.c.	2 c.c.	180 mg. in 100 c.c. water	0.330	0.211
2 c.c.	2 c.c.	170 mg. in 100 c.c. water	0.330	0.221
2 c.c.	2 c.c.	160 mg. in 100 c.c. water	0.320	0.201
2 c.c.	2 c.c.	150 mg. in 100 c.c. water	0.350	0.131
2 c.c.	2 c.c.	140 mg. in 100 c.c. water	0.222	0.103
2 c.c.	2 c.c.	130 mg. in 100 c.c. water	0.222	0.103
2 c.c.	2 c.c.	120 mg. in 100 c.c. water	0.224	0.105
2 c.c.	2 c.c.	110 mg. in 100 c.c. water	0.308	0.189
2 c.c.	2 c.c.	100 mg. in 100 c.c. water	0.247	0.128
2 c.c.	2 c.c.	90 mg. in 100 c.c. water	0.247	0.128
2 c.c.	2 c.c.	80 mg. in 100 c.c. water	0.243	0.124
2 c.c.	2 c.c.	70 mg. in 100 c.c. water	0.218	0.099
2 c.c.	2 c.c.	60 mg. in 100 c.c. water	0.221	0.102
2 c.c.	2 c.c.	50 mg. in 100 c.c. water	0.198	0.079
2 c.c.	2 c.c.	40 mg. in 100 c.c. water	0.165	0.046
2 c.c.	2 c.c.	30 mg. in 100 c.c. water	0.164	0.045
2 c.c.	2 c.c.	20 mg. in 100 c.c. water	0.140	0.021
2 c.c.	2 c.c.	10 mg. in 100 c.c. water	0.132	0.013
2 c.c.*	.....	....	0.120	
Series 2				
2 c.c.*	.....	....	0.110	
2 c.c.	2 c.c.	10 mg. in 100 c.c. water	0.141	0.030
2 c.c.	2 c.c.	9 mg. in 100 c.c. water	0.143	0.033
2 c.c.	2 c.c.	8 mg. in 100 c.c. water	0.127	0.016
2 c.c.	2 c.c.	7 mg. in 100 c.c. water	0.122	0.011
2 c.c.	2 c.c.	6 mg. in 100 c.c. water	0.118	0.007
2 c.c.	2 c.c.	5 mg. in 100 c.c. water	0.117	0.006
2 c.c.	2 c.c.	4 mg. in 100 c.c. water	0.117	0.006
2 c.c.	2 c.c.	3 mg. in 100 c.c. water	0.118	0.007
2 c.c.	2 c.c.	2 mg. in 100 c.c. water	0.111	
2 c.c.	2 c.c.	1 mg. in 100 c.c. water	0.108	
2 c.c.*	.....	....	0.113	

* Control.

TABLE 6.—Experiment 5. May 20, 1920. Urea in Water

Size of Water Sample	Urea		Blood Sugar Record, L.-B. Test
	Amount Added	Strength of Solution	
2 c.c. control	.....	....	0.040
2 c.c.	2 c.c.	300 mg. in 100 c.c. water	0.040
2 c.c.	2 c.c.	200 mg. in 100 c.c. water	0.040
2 c.c.	2 c.c.	100 mg. in 100 c.c. water	0.040
2 c.c.	2 c.c.	90 mg. in 100 c.c. water	0.040
2 c.c.	2 c.c.	80 mg. in 100 c.c. water	0.040
2 c.c.	2 c.c.	60 mg. in 100 c.c. water	0.040
2 c.c.	2 c.c.	50 mg. in 100 c.c. water	0.040
2 c.c.	2 c.c.	40 mg. in 100 c.c. water	0.040
2 c.c.	2 c.c.	30 mg. in 100 c.c. water	0.040
2 c.c.	2 c.c.	20 mg. in 100 c.c. water	0.040
2 c.c.	2 c.c.	10 mg. in 100 c.c. water	0.040

TABLE 7.—Experiment 6, May 20, 1920. Urea in Blood

Size of Blood Sample	Urea		Blood Sugar Record, L.-B. Test
	Amount Added	Strength of Solution	
2 c.c. control	.....	....	0.112
2 c.c.	2 c.c.	300 mg. in 100 c.c. water	0.113

From the above experiment it will be seen that in these amounts urea does not interfere.

Uric acid does not interfere.   Ammonia nitrogen does not interfere.

The Effect of the Amino Acids.—Glycocol: Two c.c. of water plus a knife point of glycocol.   Boiling for ten minutes produces no change.   On standing twenty minutes no change.   After complete cooling one hour and fifteen minutes, consolidation in both tubes, the glycocol tube shows a definite change.   After reheating for ten minutes the readings shown in Table 9 were obtained:

TABLE 8.—EXPERIMENT 7.   MAY 22, 1920.   THE EFFECT OF URIC ACID

2 c.c. water control...	0.040
2 c.c. water + 2 mg. uric acid...................................	0.040
2 c.c. blood control...	0.100
2 c.c. blood + 1 mg. uric acid...................................	0.100

TABLE 9.—EXPERIMENT 8.   EFFECT OF GLYCOCOL

2 c.c. water control...	0.040
2 c.c. glycocol tube..	0.190

TABLE 10.—EXPERIMENT 9.   EPINEPHRIN IN WATER

Size of Water Sample	Epinephrin		Blood Sugar Record	Water Control Record	Date and Remarks
	Amount Added	Strength of Solution			
2 c.c.	1.5 c.c.	1:1000 water	0.800	0.040	Dec. 5, 1919, open bottle epinephrin
2 c.c.	2.0 c.c.	1:1000 water	1.000		
2 c.c.	2.0 c.c.	1:1000 water	0.900	0.040	Dec. 8, 1919, new bottle epinephrin
2 c.c.	1.0 c.c.	1:1000 water	0.450		
2 c.c.	7 minims	1:1000 water	0.200		
2 c.c.	3 minims	1:1000 water	0.115		
2 c.c.	1 minim	1:1000 water	0.070		
2 c.c.	2.0 c.c.	1:1000 water	0.337	.....	March 27, 1920, epinephrin had stood in corked bottle since Dec. 8, 1919
2 c.c.	2.0 c.c.	1:2000 water	0.205		
2 c.c.	2.0 c.c.	1:4000 water	0.148		
2 c.c.	2.0 c.c.	1:5000 water	0.125	.....	New bottle May 25, 1920
2 c.c.	2.0 c.c.	1:7500 water	0.111		
2 c.c.	2.0 c.c.	1:10,000 water	0.095		
2 c.c.	2.0 c.c.	1:20,000 water	0.075		
2 c.c.	2.0 c.c.	1:50,000 water	0.060		
2 c.c.	2.0 c.c.	1:100,000 water	0.040		
2 c.c.	2.0 c.c.	1:200,000 water	0.040		
2 c.c.	2.0 c.c.	1:400,000 water	0.040		
2 c.c.	2.0 c.c.	1:800,000 water	0.040		

Tyrosin, taurin, tryptophan and alanin induce no change.   These are all the amino acids we could find.

The Effect of Epinephrin.—If a drop or two of epinephrrin solution (1 : 1,000) is added to picrate, Fehling's or Benedict's solution, a distinct reduction takes place.   The experiments tabulated in Table 10 show the lowest limit of sensitivity of the picrate solution to epinephrin in water and in blood.

The lowest limit of sensitivity in water is 2 c.c. of a 1 : 50,000 solution, or 0.00004 gm. The difference in the records obtained with the same dilution is explained by the condition of the sample, age, etc.

The experiment tabulated in Table 11 shows that epinephrin in infinitesimally small amounts induces a color change when added to blood. The lowest limit of sensitivity of the picrate solution of the Lewis-Benedict test to epinephrin added to blood is safely placed at 0.000025 per cent., or in other words, 0.025 mg. per cent. If we calculate the amount present in a 2 c.c. sample of blood plus 2 c.c. of a 1 : 4,000,000 solution, the picrate solution reacts to 0.0000005 gm. of epinephrin (adrenalin). From this it will be seen that the picrate solution is many-fold more sensitive to solutions of epinephrin added to blood than to water.

TABLE 11.—EXPERIMENT 10. APRIL 30, 1920. EPINEPHRIN IN BLOOD

| Size of Water Sample | Epinephrin | | Blood Sugar Record, L.-B. Test |
	Amount Added	Strength of Solution	
2 c.c. control	.....	....	0.127
2 c.c. control	.....	....	0.120
2 c.c.	2 c.c.	1 mg. in 100,000 c.c. water	0.196
2 c.c.	2 c.c.	1 mg. in 200,000 c.c. water	0.171
2 c.c.	2 c.c.	1 mg. in 400 000 c.c. water	0.165
2 c.c.	2 c.c.	1 mg. in 500,000 c.c. water	0.153
2 c.c.	2 c.c.	1 mg. in 1,000,000 c.c. water	0.140
2 c.c.	2 c.c.	1 mg. in 1,500,000 c.c. water	0.138
2 c.c.	2 c.c.	1 mg. in 2,000,000 c.c. water	0.136
2 c.c.	2 c.c.	1 mg. in 2,500,000 c.c. water	0.135
2 c.c.	2 c.c.	1 mg. in 3,000,000 c.c. water	0.133
2 c.c.	2 c.c.	1 mg. in 4,000,000 c.c. water	0.130
2 c.c.	2 c.c.	1 mg. in 2,000,000 c.c. water	0.160
2 c.c.	2 c.c.	1 mg. in 1,000,000 c.c. water	0.176
2 c.c. conrtol	.....	....	0.114

THE ACETONE BODIES

The Effect of Acetone.—Unless added in very large amounts, acetone in water solution produces no effect on picrate solutions. The acetone blows off. If acetone is added after heating the picrate and carbonate mixture a color change occurs with smaller amounts.

The experiments summarized in Table 15 show the sensitiveness of the picrate solution to solutions of acetone added to the blood.

It will be observed that a distinct color change occurs in the picrate solution when a concentration of 2 c.c. of a solution of 0.05 mg. of acetone in 100 c.c. of water is added to 2 c.c. of normal blood. Placing the normal acetone content of the blood at 1 or 2 mg. per liter,[4] or

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4. "Normal blood when analyzed as described for total acetone bodies yields only 1 or 2 mg. of precipitate, equivalent to from 0.013 to 0.026 gm. of acetone per liter. In diabetes as much as 2.5 gm. (250 mg.) of acetone bodies, calculated as acetone, has been observed, while patients under ordinarily good control show from 0.1 to 0.4 gm." (per liter).

TABLE 12.—Experiment 11. Dec. 8, 1919. The Effect of
Pituitary Extract

2 c.c. water control..	0.040
2 c.c. water + 1 c.c. surgical pituitary extract (pituitrin)*............	0.115
2 c.c. water + 1 drop surgical pituitary extract (pituitrin)...........	0.040
2 c.c. water + a few crystals of chlorbutanol.........................	0.342
2 c.c. water + powdered pituitary gland (P. D.).......................	0.040

* Surgical pituitary extract (pituitrin) is put up in chlorbutanol.
Pituitary extract induced no change.

TABLE 13.—Experiment 12. Thyroid Extract in Water

	Gm.,Per Cent.
2 c.c. water control.:...	0.040
2 c.c. water + 100 mg. powdered thyroid gland (P. D.)...............	0.100
2 c.c. water + 50 mg. powdered thyroid gland (P. D.)...............	0.080
2 c.c. water + 25 mg. powdered thyroid gland· (P. D.)...............	0.060
2 c.c. water + 10 mg. powdered thyroid gland (P. D.)...............	0.040
2 c.c. water + 5 mg. pwodered thyroid gland (P. D.)...............	0.040

TABLE 14.—Experiment 12. Thyroid Extract in Blood

	Gm.,Per Cent.
2 c.c. blood control...	0.125
2 c.c. blood + 100 mg. powdered thyroid gland.................	0.200
2 c.c. blood + 50 mg. powdered thyroid·gland.................	0.190
2 c.c. blood + 25 mg. powdered thyroid gland.................	0.166
2 c.c. blood + 10 mg. powdered thyroid gland.................	0.140
2 c.c. blood + 5 mg. powdered thyroid gland................·....	0.130

Thyroid extract when added to blood induces a change.

TABLE 15.—Experiment 13. Acetone in Blood

Size of Blood Sample	Acetone		Blood Sugar Record, L.-B. Test			
	Amount Added	Strength of Solution	Series 1 May 1	Series 2 May 3	Series 3 May 4	Series 4 May 13
Control	.....	....	0.113†	0.117‡	0.101§	0.103¶
2 c.c.	2 c.c.	*20 mg. to 100 c.c. water	0.250	0.210		
2 c.c.	2 c.c.	10 mg. to 100 c.c. water	0.230	0.195		
2 c.c.	2 c.c.	9 mg. to 100 c.c. water	0.230			
2 c.c.	2 c.c.	7 mg. to 100 c.c. water	0.198			
2 c.c.	2 c.c.	5 mg. to 100 c.c. water	0.185	0.180	.....	0.190
2 c.c.	2 c.c.	4 mg. to 100 c.c. wtaer	0.185	.....	.....	0.187
2 c.c.	2 c.c.	3 mg. to 100 c.c. water	0.180	.....	.....	0.193
2 c.c.	2 c.c.	2 mg. to 100 c.c. water	0.170	0.155	.....	0.189
2 c.c.	2 c.c.	1 mg. to 100 c.c. wtaer	0.150	.....	0.144	
2 c.c.	2 c.c.	0.75 mg. to 100 c.c. water	.....	0.140	0.143	0.172
2 c.c.	2 c.c.	0.50 mg. to 100 c.c. water	.....	0.135	0.135	0.170
2 c.c.	2 c.c.	0.25 mg. to 100 c.c. water	.....	0.125	0.128	
2 c.c.	2 c.c.	0.20 mg. to 100 c.c. water	.....	.....	0.127	0.144
2 c.c.	2 c.c.	0.10 mg. to 100 c.c. water	.....	.....	0.121	0.140
2 c.c.	2 c.c.	0.05 mg. to 100 c.c. water	.....	.....	0.114	

* Acetone C. P. dilutions based on specific gravity 0.797. Samples run with 100, 75, 50, 25,
15 and 10 mg. to 100 c.c. of water were practically black; no attempt was made to read them.
† Blood from a convalescent variola patient.
‡ Blood from a convalescent variola patient.
§ Blood from a normal person.
¶ The blood was taken from a boy who had an afebrile pyelitis.

from 0.001 to 0.002 mg. per cent., we are safe in saying that acetone interferes in the Lewis-Benedict test when the acetone content of the blood is increased 0.05 mg. per cent. above normal.

The remarkable sensitiveness of the picrate solution to acetone is better comprehended when we recognize the fact that in a 2 c.c. sample of blood to which is added 2 c.c. of a solution of 0.05 mg. of acetone to 100 c.c. of water, there is only 0.021 mg. (0.0000021 gm.) present.

TABLE 16.—Showing the Comparative Sensitiveness of the Lewis-Benedict Test to Solutions of Glucose in Blood and Acetone in Blood

Size of Blood Sample	Mg. Added	Record Blood + Glucose, Mg. Per Cent.	Record Blood + Acetone, Mg. Per Cent.		Record Water + Glucose, Mg. Per Cent.	Difference Between Blood + Glucose and Control, Mg. Per Cent.
2 c.c.	100	0.202	0.250		.....	0.094
2 c.c.	75	0.168	0.230		0.070	0.060
2 c.c.	50	0.152	0.230		0.053	0.044
2 c.c.	25	0.114	0.198		0.040	0.006
2 c.c.	10	0.108	0.185		0.040	0.000
2 c.c.	5	0.102	0.185		0.040	
2 c.c.	4	.....	0.180			
2 c.c.	3	.....	0.170			
2 c.c.	2	0.105	0.150			
2 c.c.	1	0.104	0.140	0.144		
2 c.c.	0.75	.....	0.135	0.143		
2 c.c.	0.50	.....	0.125	0.135		
2 c.c.	0.25	.....	•	0.128		
2 c.c.	0.20	.....		0.127		
2 c.c.	0.10	.....		0.121		
2 c.c.	0.05	.....		0.114	0.040	
Control	....	0.108	0.113	0.101		
		May 15	May 13	May 4	May 15-20	

Heavy figures show limit of sensitiveness.

TABLE 17.—Experiment 14. May 15, 1920. Glucose in Water

	Gm. Per Cent.
2 c.c. water control...	0.040
2 c.c. water + 2 c.c. 100 mg. glucose – 100 c.c. water.................	Lost
2 c.c. water + 2 c.c. 75 mg. glucose – 100 c.c. water.................	0.070
2 c.c. water + 2 c.c. 50 mg. glucose – 100 c.c. water.................	0.053
2 c.c. water + 2 c.c. 25 mg. glucose – 100 c.c. water.................	0.040
2 c.c. water + 2 c.c. 10 mg. glucose – 100 c.c. water.................	0.040
2 c.c. water + 2 c.c. 5 mg. glucsoe – 100 c.c. water.................	0.040
2 c.c. water + 2 c.c. 2 mg. glucose – 100 c.c. water.................	0.040
2 c.c. water + 2 c.c. 1 mg. glucose – 100 c.c. water.................	0.040

It may be of interest to show the comparative sensitiveness of picrate solution to solutions of glucose and solutions of acetone. Table 16 is compiled from previous experiments.

The picrate solution is sensitive to glucose in a concentration of 25 mg. per cent., to acetone in a concentration of 0.05 mg. per cent. Glucose water solutions give distinct color change at 50 mg. per cent. (Table 17).

The picrate solution used in the Lewis-Benedict blood sugar method is 500 times more sensitive to acetone than it is to glucose.

TABLE 18.—EXPERIMENT 15. MAY 21, 1920. DIACETIC ACID IN BLOOD

| Size of Blood Sample | Diacetic Acid | | Blood Sugar Record, L.-B. Test |
	Amount Added, Mg.	Strength of Solution	
2 c.c. control	...	....	0.113
2 c.c.	100	Acetic-aceto-ester in 100 c.c. water	0.256
2 c.c.	80	Acetic-aceto-ester in 100 c.c. water	0.243
2 c.c.	60	Acetic-aceto-ester in 100 c.c. water	0.251
2 c.c.	50	Acetic-aceto-ester in 100 c.c. water	0.218
2 c.c.	40	Acetic-aceto-ester in 100 c.c. water	0.210
2 c.c.	30	Acetic-aceto-ester in 100 c.c. water	0.201
2 c.c.	20	Acetic-aceto-ester in 100 c.c. water	0.195
2 c.c.	10	Acetic-aceto-ester in 100 c.c. water	0.164
2 c.c.	5	Acetic-aceto-ester in 100 c.c. water	0.147
2 c.c.	5	Acetic-aceto-ester in 100 c.c. water	0.144
2 c.c.	0.75*	Acetic-aceto-ester in 100 c.c. water	0.128
2 c.c.	0.50	Acetic-aceto-ester in 100 c.c. water	0.127
2 c.c.	0.25	Acetic-aceto-ester in 100 c.c. water	0.115
2 c.c.	0.10	Acetic-acteo-ester in 100 c.c. water	0.115
2 c.c.	0.05	Acetic-aceto-ester in 100 c.c. water	0.113
2 c.c.	0.025	Acetic-aceto-ester in 100 c.c. water	0.112

*From this point on a different sample of blood was used. The record of the control reading was inadvertently omitted from the permanent record book. It was practically the same as the first control.

TABLE 19.—EXPERIMENT 15. DIACETIC ACID IN WATER

| Size of Blood Sample | Diacetic Acid | | Blood Sugar Record, L.-B. Test |
	Amount Added, Mg.	Strength of Solution	
2 c.c. control	...	....	0.040
2 c.c.	100	Aceto-acetic-ester in 100 c.c. water	0.391
2 c.c.	80	Aceto-acetic-ester in 100 c.c. water	0.256
2 c.c.	60	Aceto-acetic-ester in 100 c.c. water	0.232
2 c.c.	50	Aceto-acetic-ester in 100 c.c. water	0.198
2 c.c.	40	Aceto-acetic-ester in 100 c.c. water	0.167
2 c.c.	30	Aceto-acetic-ester in 100 c.c. water	0.143
2 c.c.	20	Aceto-acetic-ester in 100 c.c. water	0.123
2 c.c.	10	Aceto-acetic-ester in 100 c.c. water	0.115
2 c.c.	5	Aceto-acetic-ester in 100 c.c. water	0.095
2 c.c.	4	Aceto-acetic-ester in 100 c.c. water	0.083
2 c.c.	2	Aceto-acetic-ester in 100 c.c. water	0.071
2 c.c.	1	Aceto-acetic-ester in 100 c.c. water	0.049

TABLE 20.—THE LIMIT OF SENSITIVITY OF PICRATE SOLUTION

	Gm.		Gm.
To glucose added to water is.................	0.001	Added to blood	0.0005
To creatinin added to water is...............	0.00005	Added to blood	0.00012
To diacetic acid added to water is...........	0.00002	Added to blood	0.00001
To acetone added to water is.................	....	Added to blood	0.000001
To epinephrin (adrenalin) added to water is	0.00004	Added to blood	0.0000005

TABLE 21.—THE PICRATE SENSITIVITY IN BLOOD

To creatinin is approximately..............	4 times greater than to glucose
To diacetic acid is approximately..........	50 times greater than to glucose
To acetone is approximately...............	500 times greater than to glucose
To epinephrin (adrenalin) is approximately	1000 times greater than to glucose

In these experiments the aceto-acetic-ester is hydrolyzed to diacetic acid and ethyl alcohol in the process of the test. The diacetic acid is unstable and rapidly decomposes into acetone and carbon dioxid. Ethyl alcohol also influences the picrate solution. We are safe in making the statement that diacetic acid interferes when 0.25 mg. is added to 100 c.c. of blood or when 0.00002 gm. is added to a 2 c.c. sample of blood.

DISCUSSION

We have presented a series of experiments which tend to show that blood contains substances other than sugar which induce a color change in the picrate solution employed in the modified Lewis-Benedict blood sugar method. Under normal conditions, these substances may not interfere with the established normal range for this method. Under pathologic conditions several of these substances may interfere. Those which show the most marked influence are: epinephrin, acetone and diacetic acid. Creatinin may interfere, but does so in a less marked degree if we consider the comparative sensitiveness of the picrate solution to these substances.

As picrate solution reacts to smaller quantities of acetone than are normally present in the blood, the question may well be raised: do not the acetone bodies of the blood contribute to the established normal blood sugar range for the Lewis-Benedict test? Still another question may be asked: as epinephrin in infinitesimally small quantities induce a color change in the picrate solution, is it not possible that this substance when thrown into the general circulation, as is supposed to happen in emotional states, may induce a so-called hyperglycemia without mobilizing the glycogen stores of the liver?

PARALYSIS OF THE LEFT RECURRENT LARYNGEAL NERVE ASSOCIATED WITH MITRAL STENOSIS

JOSEPH GARLAND, M.D., AND PAUL D. WHITE, M.D.

BOSTON

INTRODUCTION

A number of cases of paralysis of the left recurrent laryngeal nerve, associated with mitral disease, have been reported during the last twenty-three years. It seems probable, in view of the cases to be reported in this paper, that such a complication, as evidenced by aphonia or slight hoarseness, may be more common than is generally suspected. That this association is not more widely recognized may be due simply to the fact that the paralysis either is not noted or is not attributed to the underlying cardiac condition, and it is reasonable to suppose that, if the possibility of such a complication were borne in mind, more cases would come to light which might fit into this category.

The first mention of this condition in the literature is a report of two cases by Norbert Ortner[1] in 1897. We have found in all forty-four references on the subject, for which bibliographies can be found in the papers by Fetterolf and Norris,[2] Lian and Marcorelles,[3] Hall,[4] Permewan,[5] Lanza,[6] Carran,[7] and Quadrone.[8] In all sixty-one cases have been reported, the first thirty-seven of which have been collected and tabulated by Fetterolf and Norris in an excellent analysis of the subject. The largest single group of cases is that of eight, reported by Quadrone.

ETIOLOGY AND PATHOLOGY

The anatomic etiology of the paralysis has been the subject of some discussion, the view most widely held being that the enlarged left auricle causes pressure on the left recurrent nerve, producing either a neuritis or a pressure atrophy. In Ortner's two cases the nerve was atrophied. Fetterolf and Norris point out that the left auricular cavity expands readily only upward; posteriorly it expands against the aorta and the esophagus, anteriorly against the right auricle and the left ventricle, and below against the right auricle and the liver.

1. Ortner: Wien. klin. Wchnschr., No. 33, 1897.
2. Fetterolf and Norris: Am. J. M. Sc. **168**:625, 1911.
3. Lian, C., and Marcorelles, E.: Arch. d. mal. d. Coeur **6**:369, 1913.
4. Hall, de Haviland: Discussion at Roy. Med. Soc. London, Sect. Laryngol., May 2, 1913.
5. Permewan, W.: Ibid.
6. Lanza, L. R.: Gazz. d. osp., Milano **37**:65, 1916.
7. Carran, A., and Nunez, P. E.: Rev. med. d. Urugay, Montevideo **20**: 727, 1917.
8. Quadrone: Volumi di scritti Medici publ. in onore di Bozzolo, Torino, 1914.

Analysis of necropsy findings in the literature indicated to some authors that the etiology in seven cases was direct compression by the auricle or appendage; in two, persistent ductus arteriosus; in two, indirect compression acting on the pulmonary artery; and in one, cardiac displacement.   Fetterolf and Norris discredit the greater number of these cases, holding that, as is shown in formalin-hardened subjects, direct compression of the auricle on the nerve is practically impossible.

(after Barker)
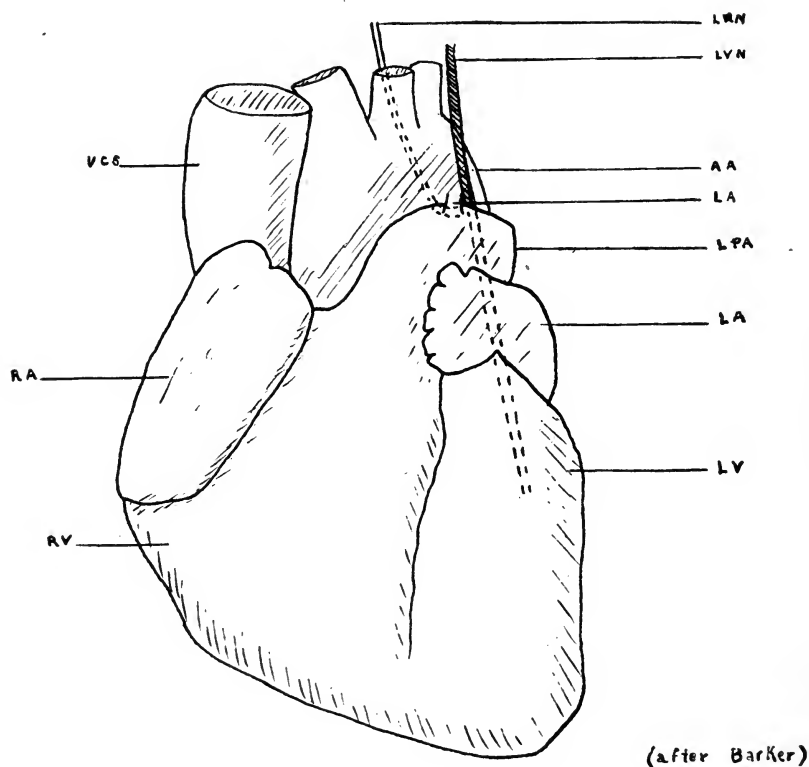
VCS, superior vena cava; RA, right atrium; RV, right ventricle; LRN, left recurrent nerve; LVN, left vagus nerve; AA, aortic arch; LA, aortic ligament; LPA, left pulmonary artery; LA, left auricle; LV, left ventricle.

The accompanying diagram shows the relation of the structures implicated, and clearly bears out the point made by these authors.   They conclude that the indirect mechanism may be variable, but when compression is accountable for paralysis, that it must always be caused by the nerve being squeezed between the left pulmonary artery and the aorta or aortic ligament, and that the paralysis is due to a pressure neuritis rather than actual destruction of the nerve.

Lian and Marcorelles set forth some of the various views on etiology which have been maintained. Ortner believed it was compression of the nerve against the aortic arch by the big left auricle; Kraus held it to be elongation of the nerve resulting from the right ventricular dilatation; Alexander, and later Fetterolf and Norris, claimed that dilatation of the left auricle acts by crowding back the pulmonary artery which is often dilated. The last named authors go on to state that in a few rare cases the voice troubles are the first symptoms which cause the patients to consult the physician who discovers the mitral stenosis. Of the eight cases of Quadrone, seven had eventually right as well as left recurrent laryngeal paralysis.

Lian and Marcorelles, Palasse, Boinet, Dmitrenko, Hofbauer, Alexander, Firschauer, and Osler used the right anterior oblique position at fifty degrees in fluoroscopy to reveal the big left auricle hidden by the spine. Lian and Marcorelles found that left lateral decubitus increased the troubles of the voice by increasing the contact of the left auricle and the pulmonary artery. A new theory which they expounded gives as a cause for the paralysis a thrombus in the left auricle or a certain degree of chronic mediastinitis, thus providing sufficient hardness for pressure.

We agree with Fetterolf and Norris that the pulmonary artery must be an intermediate agent in causing pressure, and with Lian and Marcorelles that a thrombus or a mediastinitis may occasionally be the responsible factor. Probably auricular fibrillation is an important additional factor besides the increase in size of the auricle in mitral stenosis because in auricular fibrillation the auricle remains ballooned out, with the ready production of thrombi.

Lian and Marcorelles further point out the difficulties in differential diagnosis, sufficient to render suspicious all cases not followed by necropsy. Aortic aneurysm, syphilitic mediastinitis, tracheobronchial adenopathy, esophageal cancer, and infectious or toxic recurrent neuritis must be ruled out, the roentgen ray being very important in excluding tracheobronchial adenopathy and aortic dilatation.

REPORT OF CASES

The following nine cases have been collected from the records of the past eight years of the Massachusetts General Hospital; it is probable that others, with a less marked laryngeal paralysis, have passed unnoticed:

CASE 1 (No. 185274).—H. A. L., 27, male, married. Monotype operator. Admitted Oct. 2, 1912.

Diagnosis.—Mitral stenosis. Dilated left auricle and left recurrent laryngeal nerve paralysis.

Family History.—Negative.

Past History.—Scarlet fever as a child. Fourteen years ago laid up for six weeks with pain in various joints. No redness or swelling of joints, and no fever. Patient was athletic up to two years ago.

Present Illness.—Six months ago caught cold and became hoarse. This hoarseness has persisted without remission until the present time. At the same time, he began to have some dyspnea on exertion. He stopped work seventeen weeks ago on account of dyspnea. Appetite has been lost. Slight cough for four days.

Physical Examination. — Mucous membranes cyanotic. Right pupil larger than the left.

Heart: Apex impulse felt in fifth space, 11 cm. from the midsternal line. Upper border at the second rib. Right border of dulness 4.5 cm. from the midsternal line. A blowing diastolic murmur is heard at the apex, working up into a loud presystolic roll ending in a very sharp first sound. No systolic murmur. There is a palpable thrill at the apex. The pulmonary second sound is accentuated and reduplicated. The pulses are equal, regular and synchronous.

Lungs: Numerous whistling and piping râles heard over both lungs.

Throat: Paralysis of left vocal cord. Larynx red. Left arytenoid swollen.

Wassermann: Negative.

Roentgen Ray: Marked dilatation of left auricle. Considerable peribronchial thickening with enlarged bronchial glands.

October 29: Discharged slightly relieved. Hoarseness continued.

Nov. 28, 1913: Admitted again with relapse and herpes zoster. Hoarseness present.

Discharged relieved in January, 1914. Not heard from further.

CASE 2 (No. 186950).—E. F. W., 53, female. Admitted Jan. 6, 1913.

Diagnosis.—Mitral stenosis. Auricular fibrillation. Left recurrent laryngeal nerve paralysis.

Family History.—Negative, except that one sister died of tuberculosis. Four brothers and sisters died in infancy.

Past History.—Scarlet fever in childhood. Thirty years ago questionable rheumatism in ankles and knees.

Present Illness.—Six years ago, after sudden exertion, the patient had great dyspnea and cough, with frothy, white sputum. Since that time has had dyspnea on exertion. For the last two or three years this has increased. Four years ago first noticed edema of the legs, less lately than at first. Six months ago began gradually to get hoarse. The hoarseness soon reached its maximum and has not increased since. Frequent palpitation and irregularity of the heart beat. Often has retching spells.

Physical Examination.—Mucous membranes cyanotic. Heart's apex seen and felt, diffuse and heaving, in the fifth space. Left border of dulness 16 cm. from the midline, 8 cm. to the left of the nipple. Right border of dulness, 3.5 cm. to right of midline. Sounds irregular and of poor quality. Marked systolic thrill at apex. First sound sharp. Diastolic roll at apex. Loud systolic murmur heard all over precordia, transmitted into axilla. Pulmonic second sound greater than aortic and accentuated. Pulses equal, of poor volume, low tension, and irregular in force and rhythm. Not all beats reach the wrist.

Lungs: Moist crackling râles at bases.

Liver dulness fifth space to 12 cm. below the costal border.

January 8: Discharged against advice. Not heard from further.

CASE 3 (No. 192727).—C. H., aged 48, female; watchmaker. Admitted six times between 1902 and 1916. December, 1913.

Diagnosis.—Mitral stenosis. Auricular fibrillation. "Decompensation." Hypertrophy and dilatation of the heart. Left recurrent laryngeal nerve paralysis.

Family History.—Negative.

Past History.—Chorea at 6; scarlet fever and diphtheria also in childhood.

Present Illness.—History of dyspnea, precordial pain and palpitation for past seven years.

Physical Examination.—Deeply cyanotic.

Heart: Apex impulse in sixth space, 8 cm. beyond midclavicular line. At apex there is a thrill. There are a diastolic roll and a soft blowing systolic murmur, heard loudest at the apex. Absolute irregularity of rhythm. Liver extends to 4 cm. below the costal border.

Wassermann: Negative.

Roentgen Ray: The heart shadow is very much enlarged. A bulging in region of left auricle. Diaphragm is low and limited on both sides. Apex is in seventh interspace, 10.8 cm. to left of median line. Right border is 6 cm. to right of median line. Enlarged heart with dilatation of left auricle.

Throat Consultation: Paralysis of the left recurrent laryngeal nerve.

June, 1915: Out-Patient Department. Electrocardiogram: Auricular fibrillation and right ventricular preponderance.

June, 1916: Edema and aphonia.

July, 1916: In ward again.

Died November, 1916.

CASE 4 (No. 199598).—M. E. G., aged 40, female, married, housewife. Admitted Jan. 5, 1915.

Diagnosis.—Right pyopneumothorax. Mitral stenosis. Auricular fibrillation. Left recurrent laryngeal nerve paralysis. Chronic passive congestion of the liver.

Family History.—Father, one brother and one sister died of tuberculosis.

Past History.—Inflammatory rheumatism at 17, lasting off and on for ten years. Laid up in bed three or four times for from five to six weeks with this. Chronic cough since 17 with yellowish sputum. For fifteen years has tired very easily and has had dyspnea on exertion.

Present Illness.—Nine months ago, edema of ankles; has been in bed since. During past month dyspnea has increased and cough has become more troublesome. For five days has been hoarse.

Physical Examination.—Slight cyanosis. Right pupil larger than the left.

Heart: Apex beat seen and felt in the sixth space. Supracardiac dulness 11.5 cm. in first space, 9 cm. in second space. Systolic thrill at apex. First sound sharp. Short rough systolic murmur. Diastolic roll. Soft systolic murmur at fourth left interspace. Pulmonic second sound greater than aortic and accentuated. Absolute arrhythmia.

Lungs: Right apex dull in front and dull tympany below. Moderately dull behind. Left chest, compensatory resonance. Breath sounds almost absent on right. Liver edge 5 cm. below costal border, tender. Slight edema of feet.

Wassermann: Negative.

Roentgen Ray: Hydropneumothorax on right with displacement of heart to left. Radial tracing and electrocardiogram show auricular fibrillation, the ventricular rate slowed apparently by digitalis.

Throat Consultation: Complete paralysis of left recurrent laryngeal nerve. Chest tapped several times and pus withdrawn.

January 11: Died suddenly.

Necropsy (3422).—Pyopneumothorax, right; chronic endocarditis of the mitral valve, with stenosis; hypertrophy and dilatation of the heart (414 gm.); infiltration of auricular myocardium by inflammatory cells; chronic passive congestion; hydropericardium; ascites; anasarca; arteriosclerosis of the aorta and its great branches; moderate arteriosclerosis of the pulmonary artery and its branches; cholelithiasis; old infarcts of one kidney; chronic pelvic peritonitis; chronic appendicitis; chronic pleuritis.

CASE 5 (No. 202569).—G. D. G., aged 12, male; admitted April 10, 1915.

Diagnosis.—Rheumatic heart disease with mitral stenosis. Adherent pericarditis. Left recurrent laryngeal nerve paralysis.

Family History.—Negative.

Past History.—No tonsillitis, rheumatic fever (?), or chorea.

Present Illness.—Nine years ago, as a punishment, was kept in a cold bath for half a day. After this was ill for some time, and the "body swollen." For the next two years was sick most of the time. For the next four years he was much improved. Two years ago began to have cough and dyspnea. One year ago the symptoms became worse; he was in the Children's Hospital from February to July. Three weeks ago began to have severe cough with moderate expectoration, dyspnea, palpitation, edema, and hoarseness.

Physical Examination.—Large obstructive tonsils. Moist sibilant râles all over both lungs.

Heart: Left border of dulness 10.5 cm. from midsternal line. Right border 3 cm. from midsternal line. Apex impulse shifts 2 cm. out in fifth space in left lateral position. First sound at apex snapping; long presystolic roll. At left of sternum to and fro friction rub. Short systolic murmur at second left space. Shifting dulness in flanks. Liver edge 1 cm. below costal border. Marked edema of legs. Blood pressure: Systolic, 110; diastolic, 80. Wassermann: negative.

Roentgen Ray: Seven foot plate. Apex is in the sixth space, 9.4 cm. to left of median line. Right border is 5.6 to right of median line. Total transverse diameter 15 cm. Length of heart 16.3 cm. Diameter at base 12.6 cm. Enlargement both sides of heart. Diminished pulsation. Limited excursion (?). Adherent pericarditis.

Electrocardiogram showed very large "P" deflection indicating auricular hypertrophy, normal rhythm, and right ventricular preponderance.

Throat Consultation: Partial left recurrent laryngeal nerve paralysis.

Readmitted June 21, 1915.

June 27. Twenty-six ounces clear fluid, specific gravity 1.016, removed from abdomen.

Discharged relieved, July 3.

Died at home, Oct. 1, 1915.

CASE 6 (No. 204293).—K. F., aged 26, female, single. Admitted Sept. 18, 1915.

Diagnosis.—Mitral stenosis. Paralysis of left recurrent laryngeal nerve.

Family History.—Negative.

Past History.—Measles, whooping cough, chickenpox in infancy. Many sore throats up to tonsillectomy eleven years ago. Bronchitis and grippe one year ago.

Present Illness.—Sudden attack of dyspnea three years ago with palpitation and orthopnea. Coughed a great deal; yellow sputum with blood. Since then frequent dyspnea on exertion and often orthopnea. Occasional dull pain over heart on deep breathing. Legs ache and fingernails become blue on exertion. Over-exertion induces nausea and vomiting. Since bronchitis ten months ago has had a feeling of constriction in throat and hoarseness.

Physical Examination.—Slight cyanosis.

Heart: Apex impulse seen and felt in fifth space 10 cm. to left of median line. Left border of dulness 10 cm. to left, right border 3 cm. to right of median line. Upper border at the third rib. Supracardiac dulness 5 cm. wide. Sounds regular, of fair quality. Pulmonic second sound greater than the aortic and accentuated. First apical sound very loud. There is a long diastolic murmur with presystolic accentuation in the third left interspace and at apex. The first and second sounds over the whole precordia are reduplicated.

Slight edema of the shins.

Blood Pressure: Systolic, 100; diastolic, 72.

Wassermann: Negative.

Roentgen Ray: Seven foot plate and fluoroscopy. Enlargement of both sides of the heart. Heart pulsations indistinct. About the second interspace there is a bulging from the heart shadow which does not correspond to the aortic arch and is probably the left auricle. The left lower chest is slightly duller than the right. No definite process in lung. Enlargement of heart. Apex is 10.5 cm. to left of median line. Right border 3.5 cm. Total transverse diameter 14 cm. Greatest transverse diameter of great vessels 4.5 cm. Length of heart 16 cm. Diameter at base 13.5 cm.

Electrocardiogram shows right ventricular preponderance and auricular hypertrophy (mitral stenosis). Normal rhythm.

Throat Consultation: Left recurrent laryngeal nerve paralysis.

September 29: Discharged unrelieved to Out-Patient Department.

June 7, 1916: Patient writes that she is doing well.

August, 1917: Patient writes that she is sometimes short of breath, but as a whole is better. Not heard from further.

CASE 7 (No. 208447).—D. P., aged 12, male; admitted May 18, 1916.

Diagnosis.—Acute and chronic endocarditis of aortic and mitral valves. Left recurrent laryngeal nerve paralysis. Adhesive pericarditis (?).

First entry, July 28, 1915.

Family History.—Negative.

Past History.—Negative

Present Illness.—Four weeks before first entry into hospital became very feverish and had a bad headache. In bed three weeks with dyspnea, orthopnea and palpitation. Some pain, tenderness and swelling in left knee one week ago.

Physical Examination.—Apex impulse seen and felt in fifth space 11.5 cm. from midline. Presystolic thrill at apex and palpable shock attending pulmonic second sound. Broadbent's sign present. Marked cervical and suprasternal pulsation. Left border of dulness 11.5 cm. from midline. Diastolic, presystolic and systolic murmurs heard at apex. Harsh systolic and diastolic murmurs at second left interspace and over sternum. Corrigan pulses, capillary pulse, and pistol shot in groin. Blood pressure: systolic, 144; diastolic, 10 (?). Polygram shows a long a-c interval, indicating earliest grade of block.

Roentgen Ray: Seven foot plate. Apex is 10.4 cm. to left of median line. Right border 4.3 cm. to right of midline. Total transverse diameter of great vessels is 6 cm. Length of heart, 16.7 cm. Diameter at base, 12.3 cm. Enlargement of heart especially to left.

Wassermann: negative.

Electrocardiogram: Left ventricular preponderance. Normal rhythm.

Throat Consultation: Complete paralysis of left laryngeal nerve.

Symptoms increased and there was a severe epistaxis previous to second admission. Grew rapidly worse at second entry and was taken home to die. Not heard from further.

CASE 8 (No. 214292).—A. D., aged 15, female; admitted April 11, 1917.

Diagnosis.—Rheumatic heart disease with involvement of mitral and (?) tricuspid valves. Auricular fibrillation. Adherent pericarditis (?). Left recurrent laryngeal nerve paralysis.

Family History.—Negative.

Past History.—Measles at 11.

Present Illness.—One year and nine months ago had a cold, sore throat, swollen joints, and pains all over. In bed most of time for three months and symptoms cleared up, but has had dyspnea on exertion since that time. Four months ago became more dyspneic and had edema of feet. Dyspnea has been increasing. Frequent palpitation for two years and orthopnea for three months. Four months ago, both elbows swollen, tender and painful. Three days ago edema of legs and feet began, and for three days a brassy, unproductive cough.

Physical Examination.—Heart: Apex impulse seen and felt in sixth space, 10 cm. to left of midline, in mid-axillary line, 2.5 cm. outside nipple line. Systolic thrill and heaving impulse over precordium. Left border of dulness 10 cm. to left of midline; right border 6 cm. to right; supracardiac dulness, 7 cm. Upper border of dulness at second rib. First sound not heard at apex. Aortic second sound not heard; pulmonic second sound reduplicated and accentuated. Second sound at apex preceded by loud musical systolic murmur, and followed by a short diastolic murmur. At aortic area a short blowing systolic murmur was heard. At the pulmonic area a fine musical systolic murmur. To the right of the sternum in the fifth space is a musical systolic murmur transmitted to the right axilla. Pulses small, of low tension, absolutely irregular. Liver edge, 6 cm. below the costal border. Edema over the shins. Slight cyanosis.

Wassermann: negative.

Roentgen Ray: Seven foot plate. Apex 10 cm. to left of midline. Greatest transverse diameter of great vessels 6 cm. Right border 6.5 cm. from midline. Total transverse diameter 16.5 cm. Length of heart, 16.5 cm. Diameter at base 14 cm. General enlargement of heart shadow.

Electrocardiogram: Auricular fibrillation. Right ventricular preponderance.

Throat Consultation: Paralysis of left vocal cord.

Continued with "poor compensation" until May, 1918, when he was again admitted to the ward with "decompensation" and died the following day. No necropsy.

Case 9 (No. 232912).—M. B., aged 22, female, married; admitted Sept. 29, 1919.

Diagnosis.—Mitral stenosis. Aortic regurgitation. Hypertrophy and dilatation of the heart. Paralysis of left recurrent laryngeal nerve.

Family History.—Negative

Past History.—"Double pneumonia" at birth. Many attacks of bronchitis. "Double pneumonia" at 14 with "weak heart" following. Gradual loss of weight for over a year.

Present Illness.—Felt well up to about a year ago when she became "run down." Eyesight became blurred and she had dizzy spells. Six months ago she caught cold, and raised thick yellow sputum which was occasionally blood-tinged. This lasted for six weeks. Her voice has been lost for about two months. Previously she had been hoarse for some time. She now has dyspnea on exertion and orthopnea.

Physical Examination.—Heart: Supracardiac dulness 6 cm. Left border of dulness 10 cm. to left of midline; midclavicular line 7 cm. from midline; right border of dulness 3.5 cm. to right of midsternum. Forceful impulse felt in fifth space 10 cm. to left of midline; felt also in suprasternal notch. Sounds regular, rapid and of good quality. Pulmonic second sound greater than the aortic second sound and accentuated. A long presystolic roll at the apex is followed by a sharp first sound, then a short systolic murmur. The second sound is heard. At the base are a short systolic murmur, and a short diastolic whiff, best heard over the third left interspace. The aortic second sound is heard. There is a presystolic thrill at the apex. Pulses equal, synchronous and of good volume and tension. No edema. Blood pressure: systolic, 96; diastolic, 53.

Wassermann: negative.

Roentgen Ray: Seven foot plate. The heart border is 5 cm. to the right of the median line and 7.8 cm. to the left. Total transverse diameter 12.8 cm. Length of heart 14.8 cm. Base, 11.8 cm. Total transverse diameter of great vessels is 4.4 cm. Both auricular regions are very prominent. The distance across the base is much increased. Width is somewhat increased. Appearance is that of mitral disease.

Electrocardiogram: Normal rhythm. Tachycardia. Right ventricular preponderance, and large P wave indicative of mitral stenosis.

Throat Consultation: Left vocal cord paralysis. No ulceration or other evidence of disease. October 11. Discharged unrelieved. Not heard from further.

DISCUSSION

Analysis of these nine cases shows that in Cases 1, 3 and 6 enlargement of the left auricle was shown by the roentgen ray. The right pupil was greater than the left in Cases 1 and 4. Electrocardiograms were taken in Cases 3, 4, 5, 6, 7, 8 and 9; in Cases 5, 6 and 9 auricular hypertrophy and right ventricular preponderance were found. Auricular fibrillation was present in Cases 2, 3, 4 and 8. Cases 3 and 8 also showed right ventricular preponderance by electrocardiogram. Case 4 had an extracardiac condition in the chest, displacing the entire heart. This was also the only case in which the mitral stenosis was proved by necropsy. Cases 5, 7 and 8 had possibly adherent pericarditis as well as mitral lesions. Case 2 was not roentgenographed.

The duration of the hoarseness or aphonia in the cases seen at the Massachusetts General Hospital varied from five days to ten months when the patients entered the wards; there was occasionally history of remissions.

SUMMARY

A series of nine cases of paralysis of the left recurrent laryngeal nerve associated with mitral stenosis has been found at the Massachusetts General Hospital during the last eight years. The record of but sixty-one cases in the literature, not including these nine cases, indicates that the condition is probably frequently overlooked.

THE BLOOD PICTURE BEFORE AND AFTER GOETSCH EPINEPHRIN TEST

ROSE MARY TROTT

BALTIMORE

The basis of the findings recorded here are the observations made in thirteen cases in which the Goetsch epinephrin test was applied. These cases were suggestive of thyroid disease, diagnosed as such by Drs. Baetjer and Miller. The work was carried on simultaneously with that of Cowie, and the results obtained were similar, except that Cowie's work was not done in cases diagnosed as hyperthyroidism and, therefore, did not show such a lymphocyte increase.

One of the early blood changes in toxic goiter is an increase in the ratio of lymphocytes and polymorphonuclear leukocytes and also an actual rise in the percentage of lymphocytes.

It has been shown by other observers that epinephrin administered subcutaneously will increase the leukocyte count and the erythrocyte count. In this experiment, however, the erythrocyte increase was not dwelt on. The main object was to show the change which takes place in the differential leukocyte count.

Inasmuch as epinephrin augments many of the symptoms of toxic goiter—such as rapid pulse, increased blood pressure, marked tremor, extreme weakness, sensation of heat—and produces a shaky feeling over the entire body, symptoms similar to those produced by a strong stimulant, it was thought interesting to study the blood changes after the Goetsch test and see whether the blood picture characteristic of hyperthyroidism was augmented as were the other symptoms.

This was found to be the case. Slight toxic goiter cases, with nearly normal blood picture, presented the picture of an advanced or well marked case after the administration of epinephrin.

The results compared with those of Cowie's observations on various types of persons, five of whom were normal, showed a much more marked change.

Two interesting features were brought out in this experiment: 1. The rapidity with which the blood picture was altered (in less than one hour). 2. That in practically all borderline cases, the blood picture was of normal proportions or was preceded by a leukocytosis.

The results also showed that it is evident that the blood changes under normal conditions must be, in part at least, under control of the glands of internal secretion or of the autonomic nervous system or both.

REPORT OF CASES

CASE 1.—Before the administration of 8 minims of epinephrin, the white count was 3,400. The differential count was: polymorphonuclears, 61.2 per cent.; eosinophils, 2.4 per cent.; basophils, 1.2 per cent.; small lymphocytes, 24.8 per cent.; large lymphocytes and transitionals, 10.4 per cent.

One hour later the blood count was: leukocytes, 9,800. Differential count: polymorphonuclears, 44.8 per cent.; eosinophils, 1.2 per cent.; basophils, none; small lymphocytes, 45.6 per cent.; large lymphocytes and transitionals, 8.4 per cent.

Comment: Leukopenia existed in this case before the administration of the test. The differential count was normal except for a mild basophilia. One hour after the test was made there was an increase of 6,400 leukocytes, with an absolute lymphocytosis (increase 20.8 per cent.).

CASE 2.—Before the administration of epinephrin, the leukocyte count was 5,000. The differential count was: polymorphonuclears, 60 per cent.; eosinophils, 2.4 per cent.; basophils, none; small lymphocytes, 31.2 per cent.; large lymphocytes and transitionals, 6.4 per cent.

One-half hour later, the white count was 11,000. The differential count was: polymorphonuclears, 65.2 per cent.; eosinophils, 0.4 per cent.; basophils, none; small lymphocytes, 29.2 per cent.; large lymphocytes and transitionals, 5.2 per cent.

Comment: It is noted here that while there is an increase of 6,000 in the leukocyte count there is a reduction of 2 per cent. in the lymphocytes. This patient was markedly hyperthyroid and had a mild lymphocytosis from the beginning. She reacted quite markedly to the epinephrin test, and was quite exhausted at the end of one hour, so that it was thought best not to subject her longer to the inconveniences of taking pulse, blood pressure, etc. Therefore, the count was taken at the end of one-half hour instead of the usual hour test. It is evident that the blood film was taken while the cells were undergoing the change.

CASE 3.—Before the administration of epinephrin, the leukocyte count was 8,200 and the differential count was as follows: Polymorphonuclears, 61.6 per cent.; eosinophils, 0.8 per cent.; basophils, 0.8 per cent.; small lymphocytes, 25.2 per cent.; large lymphocytes and transitionals, 11.6 per cent.

Three-quarters of an hour later, the leukocyte count was 8,100 and the differential count was: polymorphonuclears, 51.6 per cent.; eosinophils, 0.8 per cent.; basophils, 0.8 per cent.; small lymphocytes, 33.6 per cent.; large lymphocytes and transitionals, 13.2 per cent.

Comment: In this case there is no increase in the leukocyte count. There was a subsequent rise of 8.4 per cent. in the lymphocytes.

CASE 4.—Before the administration of epinephrin, the leukocyte count was 9,400 and the differential count was as follows: Polymorphonuclears, 58.8 per cent.; eosinophils, 2 per cent.; basophils, 0.4 per cent.; small lymphocytes, 29.6 per cent.; large lymphocytes and transitionals, 9.2 per cent.

Three-quarters of an hour later, the leukocyte count was 13,000 and the differential count was: polymorphonuclears, 47.2 per cent.; eosinophils, 2 per cent.; basophils, 0.4 per cent.; small lymphocytes, 42.4 per cent.; large lymphocytes and transitionals, 8 per cent.

Comment: There was a rise of 3,600 in the leukocyte count and a very marked increase in the lymphocytes—13.6 per cent.

CASE 5.—Before administration of epinephrin, the leukocyte count was 9,000 and the differential count was as follows: Polymorphonuclears, 70.8 per cent.; eosinophils, 0.8 per cent.; basophils, 0.4 per cent.; small lymphocytes, 20.4 per cent.; large lymphocytes and transitionals, 7.6 per cent.

One hour after the test was made, the leukocyte count was 13,000 and the differential count was: polymorphonuclears, 65.2 per cent.; eosinophils, 1.2 per cent.; basophils, 0.4 per cent.; small lymphocytes, 28 per cent.; large lymphocytes and transitionals, 5.2 per cent.

Comment: In this case there was an increase of 4,000 in the leukocyte count and a rise of 7.6 per cent. in the lymphocytes.

CASE 6.—Before the administration of epinephrin, the leukocyte count was 9,000 and the differential count was as follows: Polymorphonuclears, 46 per cent.; eosinophils, 2 per cent.; basophils, 0.4 per cent.; small lymphocytes, 41.6 per cent.; large lymphocytes and transitionals, 10 per cent.

Three-fourths of an hour later, the leukocyte count was 14,800 and the differential count was: polymorphonuclears, 48 per cent.; eosinophils, 0.8 per cent.; basophils, none; small lymphocytes, 47.2; large lymphocytes and transitionals, 4 per cent.

Comment: This patient was definitely hyperthyroid. There was a rise of 5,800 in the leukocyte count and an increase of 5.6 per cent. in the lymphocytes.

CASE 7.—Before the administration of epinephrin, the leukocyte count was 7,800 and the differential count was as follows: Polymorphonuclears, 75.2 per cent.; eosinophils, 0.4 per cent.; basophils, none; small lymphocytes, 17.2 per cent.; large lymphocytes and transitionals, 7.2 per cent.

Three-quarters of an hour later, the leukocyte count was 12,200 and the differential count was: polymorphonuclears, 68.8 per cent.; eosinophils, 0.4 per cent.; basophils, none; small lymphocytes, 26.8 per cent.; large lymphocytes and transitionals, 4 per cent.

Comment: In this case the leukocyte increase was 4,400 and the lymphocyte increase was 9.6 per cent.

CASE 8.—Before the administration of epinephrin, the leukocyte count was 8,400 and the differential count was as follows: Polymorphonuclears, 56.4 per cent.; eosinophils, 4.8 per cent.; basophils, 0.8 per cent.; small lymphocytes, 28.8 per cent.; large lymphocytes and transitionals, 9.2 per cent.

One-half hour later, the leukocyte count increased to 11,800 and the differential count was: polymorphonuclears, 57 per cent.; eosinophils, 3.5 per cent.; basophils, 1.5 per cent.; small lymphocytes, 30 per cent.; large lymphocytes and transitionals, 8 per cent.

Comment: In this case there was a moderate constitutional reaction to the epinephrin. The increase in the leukyocyte count was 3,400 and 1.2 per cent. in the lymphocytes.

Case 9.—Before the administration of epinephrin, the leukocyte count was 9,400 and the differential count was as follows: Polymorphonuclears, 68 per cent.; eosinophils, 1 per cent.; basophils, 1 per cent.; small lymphocytes, 20 per cent.; large lymphocytes and transitionals, 10 per cent.

Three-quarters of an hour later, the leukocyte count was 12,000 and the differential count was: polymorphonuclears, 65.2 per cent.; eosinophils, 1.2 per cent.; basophils, 0.4 per cent.; small lymphocytes, 27.2 per cent.; large lymphocytes and transitionals, 6 per cent.

Comment: There was a rise of 2,600 in the leukocyte count and an increase in the lymphocytes of 7.2 per cent.

Case 10.—Before the administration of epinephrin, the leukocyte count was 6,800 and the differential count was as follows: Polymorphonuclears, 46.4 per cent.; eosinophils, 1.2 per cent.; basophils, 0.8 per cent.; small lymphocytes, 43.2 per cent.; large lymphocytes and transitionals, 8.4 per cent.

One-half hour later, the leukocyte count was 12,600 and the differential count was: polymorphonuclears, 39.6 per cent.; eosinophils, 1.2 per cent.; basophils, none; small lymphocytes, 54 per cent.; large lymphocytes and transitionals, 5.2 per cent.

Comment: There was an increase of 5,800 in the leukocyte count and a definite rise in the lymphocytes of 10.8 per cent.

Case 11.—Before the administration of epinephrin the leukocyte count was 9,000 and the differential count was as follows: Polymorphonuclears, 64.4 per cent.; eosinophils, 0.4 per cent.; basophils, none; small lymphocytes, 29.2 per cent.; large lymphocytes and transitionals, 6 per cent.

One hour after the administration of epinephrin, the leukocyte count was 16,000 and the differential count was: polymorphonuclears, 46.4 per cent.; eosinophils, 1.6 per cent.; basophils, 0.4 per cent.; small lymphocytes, 42 per cent.; large lymphocytes and transitionals, 9.6 per cent.

Comment: There was a rise of 12.8 per cent. in the lymphocyte count, and an increase of 7,000 in the leukocyte count.

Case 12.—Before the administration of epinephrin, the leukocyte count was 10,800 and the differential count was as follows: Polymorphonuclears, 68.8 per cent.; eosinophils, none; basophils, none; small lymphocytes, 23.2 per cent.; large lymphocytes and transitionals, 8 per cent.

Three-quarters of an hour after the administration of epinephrin, the leukocyte count was 16,400 and the differential count was: polymorphonuclears, 55.2 per cent.; eosinophils, 0.4 per cent.; basophils, 0.4 per cent.; small lymphocytes, 35.6 per cent.; large lymphocytes and transitionals, 8.4.

Comment: The increase in the leukocyte count was 5,600, and the rise in the lymphocytes equalled 12.4 per cent.

Case 13.—Before the administration of epinephrin, the leukocyte count was 12,800 and the differential count was as follows: Polymorphonuclears, 64.8 per cent.; eosinophils, 0.8 per cent.; basophils, none; small lymphocytes, 26 per cent.; large lymphocytes and transitionals, 8.4 per cent.

One hour after the administration of epinephrin, the differential count was: polymorphonuclears, 48 per cent.; eosinophils, none; basophils, none; small lymphocytes, 47 per cent.; large lymphocytes and transitionals, 5 per cent. The leukocyte record was lost.

Comment: There was an increase of 21 per cent. in the lymphocyte count.

SUMMARY

The administration subcutaneously of from 4 to 8 minims of epinephrin will quickly produce a rise in the leukocyte count and cause an absolute lymphocytosis in hyperthyroid individuals. From this experiment, it is concluded that in toxic goiter an increase in the lymphocytes is not always present, especially in the borderline cases. A normal differential count is often found and in some cases a polymorphonuclear leukocytosis exists.

THE POSSIBLE PATHOGENICITY OF BACILLUS BOTULINUS *

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As commonly discussed in the literature, the danger of botulism lies entirely in the toxin produced by the organisms outside the animal body. Freed from toxin, *Bacillus botulinus* and its spores have frequently been fed or injected without loss of experimental animals. Warnings against spoiled food have commonly indicated that such foods were freed from all possible dangers of producing botulism by boiling.[1] The toxin is certainly destroyed by a brief heating at 80 C. or less. Certain strains of type B (for example the Nevin organism) and their spores are killed quickly at 100 C. More recently strains of type A (such as the Boise described by us in a recent paper [2]) have been shown to be very resistant. Clearly, a scrutiny of the organism itself as a possible source of danger was demanded. In examining suspected canned foods, *B. botulinus* has been found by us commonly associated with other resistant spore forming anaerobes, predominantly belonging to the series including *B. sporogenes* and *B. putrificus*. This group of "end-spore" formers are obligate anaerobes, produces putrefactive odors, and display so many reactions in common that animal experimentation has been necessary for the separation of the toxin forming *B. botulinus* from the less dangerous forms.

The association of these forms in food spoilage, and their common reactions establish the presumption of a common source or habitat. For some of them fecal or sewage pollution is clearly indicated. One of these (*B. sporogenes* [?]) isolated in this laboratory from well water and from food canned with it, was clearly traced to sewage of human origin. *B. botulinus* itself is reported by Kemper and Pollock,[3] and by Burke and Dickson,[4] as found in feces of swine not showing evidences of disease. Graham [5] traced cases of forage poisoning

1. Dickson: J. A. M. A. **69**:966 (Sept. 22) 1917.

2. Thom. Charles, Edmondson, Ruth B., and Giltner, L. T.: Botulism from Canned Asparagus, J. A. M. A. **73**:907 (Sept. 20) 1919.

3. Kemper and Pollock: Deutsch. med. Wchnschr. 505, 1897.

4. Burke, G. S.: The Occurrence of Bacillus botulinus in Nature, J. Bacteriol. **4**:54 (Sept.) 1919.

5. Graham, R., Himmelberger, L. R., and Pontius, R. L.: A Disease Resembling "Forage Poisoning" in Horses and Mules Wherein Oat Hay Incorporated the Primary Factor. Proc. U. S. Live Stock Sanit. Ass'n, 1915, pp. 22.

of horses to organisms belonging to type B of the *B. botulinus* group present in hen dung eaten with oats. The same results have been obtained here from hens experimentally fed with cultures of the Nevin organism by Buckley and Shippen.[6] The presence of occasional organisms of the *B. botulinus* group in the alimentary canal is thus clearly shown.

Shippen [7] working with the Nevin strain of *B. botulinus,* which he found to produce toxin freely at body temperature, records the conviction that under some conditions this strain might be expected to become pathogenic. Most of our previous experiments with feeding and inoculation of pure cultures of *B. botulinus* and its spores freed from toxin failed to produce the characteristic disease. A new series of experiments was suggested by the work of Bullock and Cramer,[8] who experimented with *B. welchii, B. tetani* and forms of similar morphology which fail to produce lesions when saline suspensions of pure cultures freed from toxin are used. They showed that if animals were inoculated with pure cultures of these forms and were injected also with small amounts of calcium chlorid, calcium nitrate, calcium acetate or sterile watery extracts of earth, lesions would develop and the characteristic toxic symptoms would follow. These authors attributed the result to the breaking down of the resistance of the host animal by the reagent injected. This phenomenon was designated "Kataplylaxis."

Our series of experiments after their method are given in detail as follows: In the first series two guinea-pigs (Nos. 1 and 2) were injected subcutaneously at the same site successively with heated spores of the Boise strain and calcium chlorid. The interval between injections was but a few minutes. The first animal received 10 mg. of calcium chlorid solution and 1 c.c. of a four months old culture of *B. botulinus* in plain milk, which had been heated at 80 C. for fifteen minutes to kill the vegetative forms and to destroy the soluble toxin. The second animal received 20 mg. of calcium chlorid and 1 c.c. of the heated spores. The check pig (No. 3) received 1 c.c. of the heated spores only. The first two guinea-pigs died of typical botulism, the first within five days, the second within four days. The check animal remained well. About twenty-four hours after the injections of calcium chlorid and spores, there was a slight swelling at the site of inoculation on all three animals. From the small ulcerlike local lesion

6. Buckley, J. S., and Shippen, L. P.: Preliminary Report on the Relation of Anaerobic Organisms to Forage Poisoning, J. Am. Veter. M. A. **50**:809, 1917.

7. Shippen, L. P.: Toxin Formation by a Variety of *B. botulinus* When Cultivated Aerobically under Various Conditions. Its Possible Production in the Animal Body, Arch. Int. Med. **23**:346 (March) 1919.

8. Bullock, W. E., and Cramer, W.: On a New Factor in the Mechanism of Bacterial Infection, Proc. Roy. Soc. Lond. Series B. **90**:513 (May 15) 1919.

of the animals which received calcium chlorid, virulent bacilli were recovered. Cultures from the liver and heart's blood of these guinea-pigs were negative for *B. botulinus.*

In the second series guinea-pigs, Nos. 4, 5 and 6, respectively, were injected at the same site at the same time with 20 mg. of calcium chlorid and 0.2 c.c. of heated *B. botulinus* spores from a dextrose beef infusion culture. The check animal received 0.2 c.c. of heated spores only. All three of the animals died of typical botulism, Nos. 4 and 6 within three days and No. 5 within four days.

In the third series of animals, Nos. 7, 8 and 9, the injections were made simultaneously at different sites, the sites were only from 3 to 4 cm. apart. The same doses were given these guinea-pigs as were given those in the above experiment. Guinea-pig No. 7 died within four days, and guinea-pig No. 8 within six days, but the check guinea-pig, No. 9, lingered on for two weeks. The organism was recovered in virulent form from the local lesion of guinea-pig No. 8, which died six days after the injection.

Spores freed from their toxin by washing were used in the fourth series. A culture of *B. botulinus* in dextrose beef infusion showing free spores was centrifuged to throw down the spores which were then washed fourteen times (in previous experiments we demonstrated the necessity of thorough washing for *B. botulinus* cells to free them completely from their toxin) in physiologic sodium chlorid solution. Two pigs (Nos. 10 and 11) were each injected successively at the same site with 0.2 c.c. of the saline spore suspension and 20 mg. of calcium chlorid. Both animals died at the end of three days. The check animal (No. 12) showed no symptoms until about the fifth day. It died on the fifteenth day of typical botulism. The local lesion and the liver of the two animals receiving calcium chlorid and spores were cultured, and virulent *B. botulinus* organisms were recovered from the local lesion only. The Boise strain was used in all of the above experiments.

In the fifth series spores from old liver broth cultures of the Nevin strain were washed twice in physiologic sodium chlorid solution, and the resulting spore suspension was heated at 80 C. for fifteen minutes, and a direct microscopic count was made by means of a Breed smear. There were 31,000,000 spores per c.c. One guinea-pig (No. 13) was then injected subcutaneously with 1 c.c. of the washed and heated spores mixed with 1 c.c. of a 2 per cent. calcium chlorid solution (20 mg.). Another animal (No. 14) was injected at different sites with the same quantities of spores and calcium chlorid. The sites were only a few centimeters apart. Another guinea-pig (No. 15) was injected with similar doses at the same site, but with an interval

of one hour between the injections of spores and calcium chlorid. Another pig (No. 16) was injected at the same site with similar doses of spores and calcium chlorid but with an interval of two and one-half days between the injections. In each case the spores were injected first. The check animal (No. 17) received an injection of 1 c.c. of the spores alone. The only animal in this series which showed typical symptoms of botulism and died was guinea-pig No. 16. Death occurred seven days after the first injection. The other animals were slightly "off" condition about a week after the injection, but this was probably the effect of the calcium chlorid. At necropsy, cultures were made from the liver and local lesion of guinea-pig No. 16. Virulent bacilli were recovered from the local lesion only.

The Boise strain was then used in Series 6. Old, liver broth cultures showing free spores were centrifuged, and the resulting sediment first washed twice in physiologic sodium chlorid solution and then heated at 80 C. for fifteen minutes. Direct microscopic count indicated 30,000,000 spores per c.c. One c.c. of the spore suspension mixed with 1 c.c. of a 2 per cent. calcium chlorid solution was then injected into a guinea-pig (No. 18). Guinea pig No. 19 was injected simultaneously with the same quantity of spores and calcium chlorid at different sites; guinea-pig No. 20 was injected at same site with an interval of one hour between the injections; and guinea-pig No. 21 at the same site with an interval of two days between the injections of spores and calcium chlorid. The check animal received 1 c.c. of spores only. Animals Nos. 18 and 20 respectively, began showing symptoms early, No. 20 within forty hours and No. 18 within forty-eight hours. The latter died four days later, but guinea-pig No. 20 died about forty-six hours after the injection. Guinea-pig No. 19 showed typical symptoms in three days, gradually got worse and died on the tenth day. Guinea-pig No. 21 and the check guinea-pig (No. 22) began showing symptoms on the third day. Six days after the injection guinea-pig No. 21 was very ill and died on the thirteenth day. The check pig died at about the same time also. At necropsy, cultures were made from the local lesion and liver of each animal. In each case virulent bacilli were recovered from the local lesions only.

The local lesion is apparently the effect of the calcium chlorid. When injected alone it produces a local inflammatory edema with more or less necrosis of the tissues at the point of injection. In some of the experimental animals there is an ulcer at the seat of injection which heals over in the course of a few weeks. The local lesion in the animals injected with both calcium chlorid and *B. botulinus* spores differs in no apparent way from that produced by the calcium chlorid

alone. There is practically no lesion where spores alone are injected. Smears made from the exudate of the local lesion of animals injected with spores and calcium chlorid showed generally only a few bacilli and many leukocytes. The leukocytes contained no bacilli. The finding of bacilli where spores were injected indicates that germination took place in the body. Smears from the local lesion of the check animal which died showed practically no organisms, but cultures revealed the presence of the bacilli in virulent form.

These experiments, which are summarized in Table 1, show that typical botulism was induced in every case where heated spores of the Boise strain were injected subcutaneously with small amounts (from 0.5 to 1.0 c.c) of a 2 per cent. calcium chlorid solution. All but two of the check pigs, which received spores only, died of botulism also, but the time interval between the deaths of those receiving spores and calcium chlorid and those receiving spores only was shortened considerably, apparently in the presence of the calcium salt. The Nevin strain gave negative results, on the whole, as only one animal died out of the four which were injected with spores and calcium chlorid. The check animal also lived. In most cases when the guinea-pigs were injected with spores and calcium chlorid at the same time at the same or different sites, death occurred in from three to six days. When two days elapsed between the injection of the spores and calcium chlorid, death was usually delayed several days.

The fact that all but two of the check animals, inoculated with spores only in the foregoing experiments died, suggested occasional pathogenicity unsupported by calcium chlorid. With this in view we repeated a number of our former experiments on the effect of the detoxified spores of *B. botulinus* in the animal body, enlarging the dose, and paying attention to the actual number of spores fed. Feeding was substituted for injection because botulism is primarily possible only by the consumption of the organisms or their toxin. These experiments given in detail are as follows.

SUMMARY OF EXPERIMENTS

Series 7.—An old culture of *B. botulinus* (Boise strain) in dextrose beef infusion showing free spores was centrifuged to throw down the spores, which were then washed three successive times in physiologic sodium chlorid solution. This saline spore suspension was heated at 80 C. for fifteen minutes, and 3 c.c. fed to a guinea-pig (No. 23). Feeding in all experiments was accomplished by introducing a pipet containing the spore suspension directly into the mouth of the animal. This pig showed no symptoms and remained well.

TABLE 1.—Effect of Injections of Calcium Chlorid and Toxin-free Spores of *B. botulinus*

Series of Experiments	Guinea-Pig No.	Subcutaneous Injections of		Strain	Site of Inoculation	Interval of Time between Injections	Death from Botulism
		CaCl₂ in Mg.	Spores				
1	1	10	1.0 (Heated at 80 C. for 15 Min.)	Boise	Same	1-2 Min.	5 days
	2	20	1.0 (Heated at 80 C. for 15 Min.)	Boise	Same	1-2 Min.	4 days
	3 (check)	0	1.0 (Heated at 80 C. for 15 Min.)	Boise	—	1-2 Min.	Remained well
2	4	20	0.2 (Heated at 80 C. for 15 Min.)	Boise	Same	0	3 days
	5	20	0.2 (Heated at 80 C. for 15 Min.)	Boise	Same	0	4 days
	6 (check)	0	0.2 (Heated at 80 C. for 15 Min.)	Boise	—	—	3 days
3	7	20	0.2 (Heated at 80 C. for 15 Min.)	Boise	Different	1-2 Min.	4 days
	8	20	0.2 (Heated at 80 C. for 15 Min.)	Boise	Different	1-2 Min.	6 days
	9 (check)	0	0.2 (Heated at 80 C. for 15 Min.)	Boise	—	—	14 days
4	10	20	0.2 (washed)	Boise	Same	1-2 Min.	3 days
	11	20	0.2 (washed)	Boise	Same	1-2 Min.	3 days
	12 (check)	0	0.2 (washed)	Boise	—	—	15 days
5	13	20	1.0 (washed and heated 31,000.000 to the c.c.)	Nevin	Same	0	Slight symptoms, recovered
	14	20	1.0 (washed and heated 31,000.000 to the c.c.)	Nevin	Different	1-2 Min.	Slight symptoms, recovered
	15	20	1.0 (washed and heated 31,000.000 to the c.c.)	Nevin	Same	1 hour	Slight symptoms, recovered
	16	20	1.0 (washed and heated 31,000.000 to the c.c.)	Nevin	Same	2½ days	7 days
	17 (check)	0	1.0 (washed and heated 31,000.000 to the c.c.)	Nevin	—	—	Remained well
6	18	20	1.0 (washed and heated 30,000.000 to the c.c.)	Boise	Same	0	4 days
	19	20	1.0 (washed and heated 30,000.000 to the c.c.)	Boise	Different	1-2 Min.	10 days
	20	20	1.0 (washed and heated 30,000,000 to the c.c.)	Boise	Same	1 hour	46 hours
	21	20	1.0 (washed and heated 30,000,000 to the c.c.)	Boise	Same	2 days	13 days
	22 (check)	0	1.0 (washed and heated 30,000.000 to the c.c.)	Boise	..	..	13 days

Another guinea-pig (No. 24) was fed with 6 c.c. of the heated spores. Six days later this guinea-pig was showing typical symptoms of botulism. It died eight days after the feeding.

Series 8.—Both the Boise and Nevin strains were used. Old cultures in liver bouillon were centrifuged to throw down the spores and the resulting sediment diluted with physiologic sodium chlorid solution and heated at 80 C. for fifteen minutes. A direct microscopic count of the saline suspension was then made by means of the Breed smear,

and 78,000,000 Nevin spores (1 c.c.) fed to one guinea-pig (No. 25) and 53,000,000 (1 c.c.) Boise spores fed to another guinea-pig (No. 26). The pig which received the spores of the Boise strain remained well, but the one which received the Nevin strain showed typical symptoms in five days and died within seven days.

Series 9.—The guinea-pigs (Nos. 27 to 32 inclusive) were fed with quantities of washed and heated spores of the two strains. The count for each strain was 50,000,000 spores per c.c. As checks two guinea-pigs for each strain were injected respectively with 1 c.c. of supernatant liquid from heated centrifuged spores and with 1 c.c. of unheated spores. Cultures made from the heated supernatant liquid showed slight growth after several days, showing that all the spores had not been thrown down in the centrifuge. However, for practical purposes, it was assumed that the liquid was free from spores. The Nevin pig (No. 27) which was fed 50,000,000 spores remained well but the Boise guinea-pig (No. 30) showed symptoms on the second day and died seventeen days after the feeding. Virulent bacilli were recovered from the liver of this animal. The check guinea-pigs which received supernatant liquid from heated, centrifuged spores remained well. The two checks on the virulence of the cultures, that is, the animals which received 1 c.c. of unheated spore suspension, died in about eighteen hours. The difference in time is striking.

Series 10.—Doses of 75,000,000, 100,000,000 and 112,500,000, respectively, of washed and heated spores from Nevin strain cultures were fed to guinea-pigs Nos. 33, 34, and 35, respectively, with no ill results. The check guinea-pig (No. 36) which received an intraperitoneal injection of 1 c.c. of supernatant liquid from the centrifuged heated spores also remained well.

Series 11.—The dose of spores was increased. Six c.c. of a washed and heated spore suspension from a culture of the Boise strain, containing 180,000,000 spores to the c.c. were fed to guinea-pig No. 37. The check, No. 38, received an intraperitoneal injection of 1 c.c. of the supernatant liquid from a portion of the centrifuged heated spores. Guinea-pig No. 37 died of typical botulism within five days but the check animal remained well. At necropsy a culture was made from the liver of guinea-pig No. 37 but the organism was not recovered.

Series 12.—In the next experiment small and large doses of Boise spores were fed to guinea-pigs Nos. 39 and 40 respectively. The small dose consisted of 32,000,000 spores in salt solution, the large dose consisted of 192,000,000. The check animal (No. 41) as before received 1 c.c. of supernatant liquid from a portion of the centrifuged, washed and heated spores. The guinea-pig which received the small

dose showed no symptoms but the one which received the large dose showed symptoms in about two days and died seven days after feeding. The check animal remained well.

TABLE 2.—EFFECT OF FEEDING TOXIN-FREE SPORES OF *B. botulinus*

Series	Guinea-Pig	Strain of B. Botulinus	Dose of Heated Spores		Death from Botulism
			No. C.c.	No. Spores to C.c.	
7	23	Boise	3.0	No count was made	Remained well
	24	Boise	6.0	No count was made	8 days
8	25	Nevin	1.0	78,000,000	7 days
	26	Boise	1.0	53,000,000	Remained well
9	27	Nevin	1.0	50,000,000	Remained well
	28 (check)	Nevin	1.0	Injection of super-natant liquid from centrifuged spores	Remained well
	29 (check)	Nevin	1.0	Injection of 50,000,000 unheated spores	18 hours
	30	Boise	1.0	50,000,000	17 days
	31 (check)	Boise	1.0	Injection of super-natant liquid from centrifuged spores	Remained well
	32 (check)	Boise	1.0	Injection of 50,000,000 unheated spores	18 hours
10	33	Nevin	1.5	75,000,000	Remained well
	34	Nevin	2.0	100,000,000	Remained well
	35	Nevin	2.25	112,500,000	Remained well
	36 (check)	Nevin	1.0	Injection of super-natant liquid from centrifuged spores	Remained well
11	37	Boise	6.0	180,000,000	5 days
	38 (check)	Boise	1.0	Injection of super-natant liquid from centrifuged spores	Remained well
12	39	Boise	0.5	32,000,000	Remained well
	40	Boise	3.0	192,000,000	7 days
	41 (check)	Boise	1.0	Injection of super-natant liquid from centrifuged spores	Remained well

In general, the experiments with the Boise strain were consistent. Small doses of heated spores produced no effect when fed to guinea-pigs but large doses promptly caused botulism. Again the experiments with the Nevin organism were unsatisfactory. In one case a dose of only 78,000,000 spores caused death but in other cases doses of 100,-000,000 and 112,500,000 spores failed to produce botulism. These results, summarized in Table 2, while irregular, confirm the discrepancies in our former experiments with the detoxified bacilli or spores of *B. botulinus*. They show that occasionally the guinea-pigs will develop the specific disease and die when fed or injected with large doses of the spores freed from toxin in routine manner. Just what conditions in the animal body favor the growth of the organism are not known. It is quite possible that botulism, when it occurs in such cases, is the result of the absorption of intracellular toxin which is protected during the heating process by the highly insulated spore wall and released in the body upon the dissolution of the spore wall, or,

on the other hand, it may be that the spores actually germinate in the animal body, probably in the small intestine and produce the toxin there. Experiments on this phase of the question are contemplated.

GENERAL DISCUSSION

The fundamental importance of knowing more about these toxin-forming anaerobes is brought out by these results. The line between pathogenicity and saprophytism is not a sharp one. Our conception of species in bacteria is equally hazy. *Bacillus botulinus* as a species very clearly consists of a series of strains or varieties with a common morphology and a common ability to produce particular toxins. These strains differ in details of reactions. Van Ermengem evidently possessed a form which produced toxin slightly, if at all, at body temperature. The Nevin organism (type B) as studied by Shippen grows and produces toxin freely at 37 C. Both are equally easily killed by boiling. The Boise strain, one of the Type A series, is resistant to high temperatures and in addition finds its optimum development at body temperature.

This combination of toxin forming power and optimum growth at body temperature called for continued investigation of the possibilities of pathogenicity for some at least of these strains. Although the organism was considered a strict saprophyte, occasional deaths of check animals occurred under conditions difficult to interpret. Search for explanation of these cases led to the experiments here reported. It has been shown that *B. botulinus* will produce botulism in experimental animals if calcium chlorid is injected with toxin-freed spores as described by Bullock and Cramer, for *B. welchii* and its allies. In this respect, therefore, *B. botulinus* reacts in the same way as the organisms of gas gangrene and tetanus studied by these authors. A limited pathogenicity is thus established.

This increased evidence of pathogenicity led to the subsequent series of feeding experiments, using large quantities of *B. botulinus* spores. The large number of deaths among these experimental animals gives additional warning of the dangerous character of the organism itself.[9] These results decrease our confidence in the effect of ordinary heating as a means of freeing suspected foodstuffs from possible danger.

SUMMARY AND CONCLUSIONS

1. Calcium chlorid acts as an accessory factor in producing botulism when injected into guinea pigs with toxin-freed bacilli or spores of

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9. These results obtained independently are in agreement with those of Paul F. Orr: Some Observations on the Biological Characteristics of *B. botulinus* and Its Toxins, Abstr. Bacteriol. **4:** (Feb.) 1920.

B. botulinus. Under such conditions the behavior of *B. botulinus* is similar to that reported by Bullock and Cramer for the organisms of gas gangrene and tetanus.

2. On the basis of experiments tried, toxin-freed spores of the Boise strain of *B. botulinus,* when fed in sufficiently large doses to guinea-pigs, can produce the specific disease and death, while the Nevin strain similarly fed does so occasionally. A limited pathogenicity is thus indicated.

3. Foods suspected of containing *B. botulinus* should be destroyed, not heated and eaten.

A STUDY OF THE RENAL CONCENTRATION POWER FOR URIC ACID IN EARLY CHRONIC INTERSTITIAL NEPHRITIS

SECOND PAPER

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BROOKLYN

In a previous communication we presented a preliminary report of our work regarding the concentration power of the kidney for uric acid in early chronic interstitial nephritis. By the term interstitial nephritis was meant the renal anatomic lesion which is commonly associated with that condition. The cases presented as positive nephritis were only such as could readily be diagnosed by the conventional methods. It was shown that in such the renal concentration power for uric acid was markedly lowered, while in normal individuals no such lowering took place. A number of cases were also recorded in which a positive diagnosis of nephritis could not be made by the conventional methods. These cases, however, gave many suspicious symptoms of nephritis, and were, therefore, listed as questionable nephritis. They all showed lowering of the renal function for uric acid, and the thought was expressed by us that they were in reality positive nephritis as their further development would prove. In continuing the general study, we have made observations of the renal concentration power for uric acid in a number of diversified conditions. It has developed that the findings thus obtained are of crucial importance in the application of the method to the diagnosis of early chronic interstitial nephritis. A consideration of their significance is hence now undertaken.

METHOD OF COMPUTING RENAL CONCENTRATION POWER

In our preliminary work the renal concentration power was computed by merely dividing the amount of urine uric acid per hundred c.c. by the amount of blood uric acid per hundred c.c., both specimens having been taken simultaneously. The renal concentration power for any given substance is represented by the concentration of that substance in the urine. The concentration of any substance in a fluid is represented by the amount of that substance which is contained in a given volume of the fluid. In our original method of computation, the volume of urine was kept stationary at 100 c.c., the amount of

uric acid in such a volume varying as the conditions altered. It is evident that such a method of computation might be liable to certain inaccuracy since only one of the factors concerned in concentration is variable (namely, the amount of uric acid), the other factor (namely, the volume of fluid) being kept stationary. In order to obviate this error we have in the present communication adopted the formula recently proposed by Van Slyke for the above purpose. We do not here enter into a discussion of the Van Slyke method of computation but refer all interested to his original communication.[1]

In comparing Van Slyke's formula with our original method in the cases herein reported, a material difference in result occurred in about 10 per cent. of the cases.

AMOUNT OF BLOOD URIC ACID NOT A GUIDE TO THE RENAL FUNCTIONAL ACTIVITY FOR URIC ACID

In our preliminary communication we drew attention to the fact, which was deducted from the cases therein reported, that the mere amount of blood uric acid was not necessarily a guide to the renal functional activity for uric acid. This, of course, means that estimations of blood uric acid are unreliable for the judgment of the uric acid renal function. We desire here to emphasize this point and to add further proof thereof.

Table 1 shows a number of cases in which the blood uric acid was high, but the blood renal uric acid co-efficient was normal, showing a normal renal function for uric acid. This table further shows that when these cases were placed on a purin free diet, the blood uric acid promptly fell to normal.

TABLE 1.—Cases with Normal Renal Function for Uric Acid

Patient	Ordinary Diet		Purin Free Diet	
	Blood Uric Acid Mg. per 100 c.c.*	Coefficient†	Blood Uric Acid Mg. per 100 c.c.*	Coefficient†
H. W. H...............	6.47	2.6	2.90	2.8
C. M..................	6.82	2.9	2.87	3.1
F. G..................	7.20	3.2	3.00	3.7
C. A..................	7.67	3.8	2.60	4.6
A. A..................	5.80	2.6	2.10	2.9

* Normal blood uric acid per 100 c.c., 1 to 3 mg.
† Normal coefficient, 2.4 to 4.7 mg.

Table 2 contains cases in which the blood uric acid was high, but in which the blood renal uric acid co-efficient was low, showing a reduced

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1. Proceedings of the American Society of Experimental Medicine and Biology, December, 1919.

renal function for uric acid. Table 2 also shows that when these cases were placed on a purin free diet, the blood uric acid was not brought to normal.

TABLE 2.—CASES WITH REDUCED RENAL FUNCTION FOR URIC ACID

Patient	Ordinary Diet		Purin Free Diet	
	Blood Uric Acid Mg. per 100 c.c.*	Coefficient†	Blood Uric Acid Mg. per 100 c.c.*	Coefficient†
F. W.....................	6.62	1.4	4.97	1.5
F. W.....................	7.94	0.92	6.01	0.96
A. D.....................	7.32	0.84	6.30	0.87
M. L.....................	6.46	1.1	5.20	1.3
W. H.....................	6.95	1.6	5.15	1.7

* Normal blood uric acid per 100 c.c., 1 to 3 mg.
† Normal coefficient, 2.4 to 4.7 mg.

The response and nonresponse of the blood uric acid to diet in these two classes of cases appears to us to be absolute proof that the blood renal uric acid co-efficient is the correct index of the renal functional activity for uric acid and that the mere blood amount of uric acid is no such guide. Both classes gave high figures for blood uric acid and from these figures alone it could not have been judged whether or not there was present a reduced renal uric acid function. We feel that this point needs emphasis because it has been and is now the prevalent practice on the basis of mere blood estimations of uric acid to make diagnosis for or against a reduction of renal function. It is certain such procedure frequently leads to erroneous conclusions which have confused the clinician and caused dissatisfaction.

REPORT OF CASES

In studying the results of our investigation it has developed that many cases of reduced renal function for uric acid cannot be accounted for from a clinical standpoint by a diagnosis of nephritis. Thus many cases in which a clinical diagnosis of nephritis is not possible, show such a reduction. The fundamental questions for consideration relate to the genesis and significance of such reduced function. It would seem possible that such genesis and significance might be as follows:

Due either to errors in diet or from a variety of perverted body functions existing over a shorter or longer period of time there occurs an excessive supply to the blood of various end products of which uric acid is one. In this way the kidney is put under stress of excessive elimination. Since it is a physiologic law that the body organs in general respond to stimulation, so at first there is probably a period of increased renal function. As time goes on, however, and repeated

TABLE 3.—Uric Acid Retention Due to Varying Causes

No.	Name	Age	Blood Pressure	Cardiac Area Verified by Roentgenograms	Cardiac Murmur	Brachials	Headache	Vertigo	Vision	Eye Ground	Loss of Weight	Digestive Disturbances	Edema	Albumin	Casts	Blood Uric Acid,* Mg. per 100 C.c.	Urine Uric Acid,* Mg. per 100 C.c.	Renal Concentration	Etiologic Types
1	M. N.	26	90				+	+	+		+	+				10.14	35.38	0.96	Endocrine
2	M. S.	33	180	+			+	+	+		+	+		+	+	4.4	25.00	1.00	Endocrine
3	J. J. D.	45	128	+			+	+	+		+	+				9.46	74.00	1.1	Uric acid
4	J. J. D.	48	110	+			+	+	+			+				6.10	30.00	1.4	Uric acid
5	C. W.	35	120	+			+	+	+		+	+		+		11.70	57.50	0.51	Poor metabolism
6	L. B.	34	140	+	+		+	+	+	+	+	+		+		15.15	26.40	0.35	Uric acid
7	G. G.	28	90				+	+	+	+	+	+		+		4.88	53.50	1.8	Poor metabolism
8	H. P. B.	43	90		+		+	+	+		+	+		+		6.18	45.00	1.00	Poor metabolism
9	N. W.	52	120	+	+		+	+	+							7.7	53.50	1.00	Arteriosclerosis
10	T. C.	68	180	+	+	+	+	+	+	+	+	+		+		6.18	19.70	0.86	Arteriosclerosis
11	R. F. F.	38	180	+	+	+	+	+	+	+	+	+				10.60	40.80	3.4	Arteriosclerosis
12	G. R.	48	128	+	+	+	+	+		+	+	+				3.46	15.40	1.00	Def. Dig. function
13	W. R. L.	28	126			+	+	+		+	+	+				3.88	14.42	1.8	Def. Dig. function
14	J. W.	63	150		+	+	+	+		+		+				4.44	37.50	1.3	Pernicious anemia
15	J. L. M.	27	110	+	+		+	+		+		+		+		8.25	10.50	0.16	Def. Dig. function
16	J. W. P.	38	90	+	+		+	+				+				8.08	15.05	0.43	Def. Dig. function
17	S. G.	18	110	+	+		+	+				+				6.20	20.40	1.2	Def. Dig. function
18	R. W.	38	140				+	+				+		+		5.05	40.25	1.9	Def. Dig. function
19	R. P. S.	41	170	+	+			+				+				5.5	66.00	1.3	Def. Dig. function
20	F. W. G.	34	128	+	+		+	+				+				6.15	1.08 †	1.3	Def. Dig. function
21	M. A. F.	44	120	+	+		+									6.50	0.642	1.08	Def. Dig. function
22	G. McG.	53	140								+	+				5.75	0.247	0.60	Def. Dig. function
23	J. A.	53	180	+	+	+						+				5.00	0.592	0.89	Def. Dig. function
24	J. E. B.	43	120									+				2.52	0.688	2.60	Def. Dig. function
25	B. L.	32	100					!			+	+		+		3.00	0.435	1.00	Def. Dig. function

* Normal blood uric acid per 100 c.c. 1 to 3 mg.
† All names following are gm. per twenty-four hours.

TABLE 4.—Chronic Interstitial Nephritis

No.	Name	Age	Blood Pressure	Cardiac Area Verified by Roentgenograms	Cardiac Murmur	Brachials	Headache	Vertigo	Vision	Eye Ground	Loss of Weight	Digestive Disturbances	Edema	Albumin	Casts	Blood Uric Acid, Mg. per 100 C.c.	Urine Uric Acid, Mg. per 100 C.c.	Renal Concentration
1	A. W. A.	49	170	+		+	+	+	+	+					+		3.16	38.8	6.2
2	A. W. B.	60	170	+	+	+	+	+	+	+		+					6.27	22.0	11.2
3	J. B.	65	170	+	+	+	+	+	+	+				+			5.06	36.25	1.0
4	H. K.	38	142				+	+	+		+	+					7.86	18.72	0.74
5	V. A.	58	154	+	+	+	+	+	+		+	+		+	+	7.65	51.3	1.8
6	J. J.	51	200	+	+	+	+	+	+		+	+		+	+	6.79	46.9	6.9
7	H. H.	14	110				+	+			+	+				4.00	56.00	0.95
8	H. B. D.	38	108				+	+	+		+	+				7.12	35.7	5.0
9	M. T.	46	150				+	+	+		+	+		+		2.94	18.75	1.8
10	H. R. M.	61	120				+	+	+		+	+		+		5.74	55.00	1.1
11	R. G. Y.	33	168			+	+	+	+		+	+				9.24	30.87	0.53
12	A. B. H.	33	110				+	+		+	+	+			+	4.58	1.02	0.067
13	B. M.	50	90	+	+	+	+	+			+	+				4.62	24.00	0.53
14	A. E. M.	52	200	+	+	+	+	+	+		+	+		+		9.15	18.45	0.39
15	G. P.	28	110				+	+			+	+		+	+	1.90	46.6	3.6
16	E. A.	28	110				+	+	+		+	+				6.69	93.5	1.3
17	R. F. T.	60	130	+	+	+	+	+	+		+	+				10.60	40.80	0.66
18	R. T. S.	45	108	+	+	+	+	+	+	+	+	+				7.86	6.48	0.18
19	C. L.	52	110	:	:	:	:	:	:	:	:	:	:	:	:	5.08	16.30	0.82
20	G. R. W.	..		+	+	+	+	+	+		+	+				....	†	0.09
21	A. M. H.	67	180	+	+	+	+	+	+	+	+	+		+		6.70	1.27	0.59
22	E. W. H.	5.5	180	+	+	+	+	+	+	+	+	+				6.00	0.45	0.58
23	J. A. P.	51	190	+	+	+	+	+	+					+		5.55	0.45	1.4
24	M. B.	57	150				+			+	+			+		6.50	2.32	1.1
25	E. H.	58	200	+	+	+	+	+	+	+	+	+				8.10	5.37	0.97
26	E. B.	60	190	+	+	+	+	+	+		+	+	+			5.08	0.386	0.50
27		78	200														1.87	0.25	

* Normal blood uric acid per 100 c.c. from 1 to 3 mg.
† All names following are gm. per twenty-four hours.

onslaughts are made on the renal function, such function falters with a concurrent increase of the amount of blood uric acid. Whether such faltering is due to renal anatomic changes and is in reality the initial stage, hitherto unrecognized, of an anatomic nephritis is a question which can only be decided by a considerable number of coincident blood examinations and necropsy investigations. If such should prove true, an anatomical nephritis as it has been understood is a terminal symptomatology of a process of perverted metabolism or dietary errors. We would not be understood as thinking that the above would offer the only explanation of nephritic genesis, for the casual relation of bacterial toxins and other toxic substances to nephritis has been advanced on logical grounds. In such cases it is evident that the primary excitant of the reduced renal function is the local effect on the kidney of these toxic substances.

From these cases it is seen that a reduced renal function for uric acid is present in a variety of conditions other than an anatomic nephritis—the presence or absence of such anatomical nephritis being decided by the conventional methods. If, however, the foregoing reasoning has any basis in fact the discovery of the reduced renal function is of prime importance.

For, from the standpoint of treatment and prognosis the causes of the reduced renal function must be ascertained and corrected.

The discovery of reduced renal uric acid function, therefore, while it does not give by itself a diagnosis of anatomical nephritis, is of much greater value than if such were the case. This is so because it is an early sign of kidney damage, often occurring before a clinical diagnosis of an anatomical nephritis can be made.

The practical application from a clinician's standpoint in treating these cases of low uric acid co-efficients has been by three methods. First, by the reduction of the purin diet; second, by increasing the cardiac function, and, third, by therapeutic methods toward increasing renal elimination. The results obtained were extremely satisfactory at times, sometimes with the use of one method, other times with the use of the second method or by the combination of one or more methods. But other cases failed to show improvement and from a study of these cases we were led to believe that it was due to a second factor of retention in the blood, and it is along this line that our investigations of the second substance or possibly three substances of retention is being made. Thus our studies are not being limited to blood uric acid alone, but at the present time are including other substances of blood chemistry.

HYMENOLEPIS NANA; POSSIBLE CERCOCYSTIS STAGE *

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Since the prediction of Stiles [1] that *Hymenolepis nana* would prove to be a common intestinal parasite in the United States, cases have been reported with increasing frequency, and the indications are that it is the most common tapeworm in many parts of the United States.

Ransom [2] compiled the United States cases up to 1904, reporting twenty-five cases, all but one of the twenty-five having been reported after 1902.

Deaderick, [3] in reporting two new cases in 1910, found that the number had reached thirty-three.

Schloss [4] in the same year reported twenty cases of *Hymenolepis nana* in 280 children examined for intestinal parasites and only five cases of *Tenia saginata*.

Amesse [5] reported one case from Professor Howland's service at Bellevue Hospital.

M. A. Wood [6] reported three cases of *Hymenolepis nana* from Houston, Texas.

Bass and Gage [7] reported fifteen cases out of 577 persons examined in New Orleans, and only three cases of *Tenia saginata*.

H. B. Wood, [8] from records of examinations made during 1911 and the first quarter of 1912 in the state laboratories of the South, found *Hymenolepis nana* in 1,004 of 62,785 persons examined, and only ten cases of *Tenia saginata*.

Deaderick and Thompson [9] stated that during 1911-1913, of 56,543 infections found by the Rockefeller Sanitary Commission, 1,879, or 3.3 per cent., were dwarf tapeworm.

1. Stiles, C. W.: New York M. J. **77**:877 (Nov. 7) 1903.
2. Ransom, B. H.: U. S. P. H. Service, Hyg. Lab. Bull. **18**: 1904.
3. Deaderick, W. H.: Arch. of Schiffs u. of Trop. Hyg. **14**:21, 1910.
4. Schloss, O.: Am. J. M. Sc. **139**:675, 1910.
5. Amesse, J. W.: Colorado M. **7**:483, 1910.
6. Wood, M. A.: Texas State J. M. **6**:144, 1910.
7. Bass, C. C., and Gage, J. W.: New York M. J. **92**:769 (Oct. 15) 1910.
8. Wood, H. B.: J. A. M. A. **59**:1707 (Nov. 9) 1912.
9. Deaderick, W. H., and Thompson, L: The Endemic Diseases of the Southern States, p. 503.

Gerber [10] reported the first case from Boston.

Judkins [11] found seventy-one cases among 15,000 people examined throughout Texas.

McNeil [12] reported six cases of *Hymenolepis nana* in the Southern Pacific Hospital in Houston, Texas.

Greil [13] found seventy-five children under twelve years of age in Montgomery, Ala., with dwarf tapeworm infection.

Frey [14] reported that out of 118 cases of parasite infections in the Texas State Orphan Home, 32.6 per cent. were *Hymenolepis nana.*

Van Liere [15] reported one case in twenty foreign students examined at the University of Wisconsin.

Willets [16] reported six cases in the Georgia State Sanitarium.

Lyon,[17] in a study of 477 patients at the Walter Reed General Hospital, found two cases of dwarf tapeworm and five cases of *Tenia saginata.* The latter, however, were diagnosed before being referred to the hospital.

Kofoid and Kornhauser [18] examined the stools of 1,200 American soldiers who had been overseas and of 300 home service men. In the former series there were seven cases of *Hymenolepis nana;* in the latter none.

DeBuys [19] studied 595 children from seven different institutions in New Orleans, and found *Hymenolepis nana* in fifty-five cases, or 9.25 per cent. No other tapeworms were found.

Lucke [20] reported 230 cases of dwarf tapeworm in 35,000 white and black troops at Camp Zachary Taylor, Kentucky. *Tenia saginata* was found twelve times.

Notwithstanding the fact that the parasite has been one of the most frequently encountered, according to the reports of several authors, yet in many localities *Hymenolepis nana* has either not been looked for or has not been found. So far as is known there are no case reports from the region of St. Louis.

The following cases occurred in that city in the B. family, colored. The family came to St. Louis from Mississippi early in 1917. There were eight children, seven of whom were infected with the dwarf

10. Gerber, I.: Boston M. & S. J. **168**:346 (March 6) 1913.
11. Judkins, O. H.: Texas State J. M. **10**:126 (July) 1914.
12. McNeil, H. L.: Southern M. J. **8**:486 (June 1) 1915.
13. Greil, G. J.: Am. J. Dis. Child. **10**:363 (Nov.) 1915.
14. Frey, J. H.: Texas State J. M. **11**:229, 1915.
15. Van Liere, E. J.: J. A. M. A. **67**:1369 (Nov. 4) 1916.
16. Willets, D. J.: Southern M. J. **10**:42 (Jan. 1) 1917.
17. Lyon, M. W.: J. A. M. A. **72**:326 (Feb. 1) 1919.
18. Kofoid, C.; Kornhauser, S., and Plate, J. T.: J. A. M. A. **72**:1721 (June 14) 1919.
19. DeBuys, L. R., and Dwyer, H. L.: Am. J. Dis. Child. **18**:269 (Oct.) 1919.
20. Lucke, B.: Mil. Surgeon **44**:620 (June) 1919.

tapeworm and the eighth with *Ascaris lumbricoides*. The mother had pin worms, the father was free from parasites. The first patient was sent into Barnes Hospital from the out-patient pediatric service; the others were seen at their home.

REPORT OF CASES

Case 1.—F. B., male, aged 5 years, born in Mississippi. Entered Barnes Hospital, Jan. 19, 1920, on account of severe diarrhea. In October, 1919, he began having numerous loose mucoid stools with blood, sometimes bright red, sometimes tarry. Considerable straining at stool, no vomiting or pain; appetite greatly increased. Physical examination showed moderate distention of abdomen. Red blood cells, 4,160,000; hemoglobin, 80 per cent.; eosinophilia, 7 per cent. Stool was liquid, light yellow, with mucus, benzidin positive; very many ova of *Hymenolepis nana*.

Treated with male fern January 21; no worms recovered. Stools egg free up to January 28, an interval of seven days. Treatment repeated February 10 and at least one thousand *Hymenolepis nana* worms were obtained. Stools were egg free up to February 23, when many small circular bodies from 5 to 15 microns in diameter were observed. February 24, thymol, 15 grains, was given, and one worm was found. Stools egg free to March 15, an interval of eleven days. March 19 male fern was given but vomited, and March 20 another dose was given through a tube. Many tags of tissue containing heads of dwarf tapeworm embedded within the tissue were found. No whole worms or segments were observed. Stools egg free to March 29, an interval of ten days. Discharged from hospital April 4. Stool on discharge, soft, brown, little mucus, no blood; dwarf tapeworm eggs, from 1 to 3 per low power field. April 18, condition good; stool as on April 4. May 28, patient had had measles in interim and was very anemic; passing considerable blood in stools. Stool was soft, yellow and blood streaked and contained large numbers of *Hymenolepis nana* eggs.

Case 2.—J. B., male, aged 1 year 7 months, born in St. Louis. February 22, no symptoms; physical examination negative; stools hard, brown, few *Hymenolepis nana* eggs found; eosinophils, 3 per cent.

Case 3.—E. B., female, aged 3 years, born in Mississippi as were all the others. All through January had four or five loose stools a day. For the past four months has frequently had similar symptoms. Complains of abdominal pain during these periods. February 22, stool gray-brown, much mucus, many *Hymenolepis nana* eggs; eosinophils, 6 per cent.

Case 4.—A. B., female, aged 8 years. At 3 years passed twenty-three ascarides (?). Occasional short attacks of diarrhea for past four months, with abdominal pain. Nausea and vomiting, frequently with dizziness. Patient is anemic and drowsy. Hemoglobin, 70 per cent.; red blood cells, 3,500,000; white blood cells, 9,000; eosinophils, 9 per cent. February 22, stool soft, gray, with considerable mucus. Very many *Hymenolepis nana* eggs. March 29, course of male fern. Several thousand *Hymenolepis nana* worms obtained. April 17, general condition good; no symptoms since treatment. No *Hymenolepis nana* eggs found in stools.

Case 5.—A. B., male, aged 8 years. Complains of frequent frontal headaches. Examination negative; eosinophils, 3 per cent. February 22, stool normal; no eggs found in preparations. March 27, very many *Hymenolepis nana* eggs.

Case 6.—R. B., male, aged 9 years. No symptoms; physical examination negative; eosinophils, 2 per cent.; stool normal; few *Hymenolepis nana* eggs.

Case 7.—M. B., female, aged 11 years. For the past year has had attacks of diarrhea, the last one early in February. Frequently has tenderness in abdomen and gets dizzy at times. Recalls no symptoms previous to past year.

Patient anemic; has slight abdominal tenderness. February 22, stool normal; very many *Hymenolepis nana* eggs. Eosinophils, 7 per cent.; red blood cells, 3,800,000; white blood cells, 8,000. March 29, course of male fern; at least one thousand worms obtained. April 17, few *Hymenolepis nana* eggs found. No symptoms since treatment.

The morphology of the worms does not differ essentially in any respect from the usual descriptions. Specimens were sent to Dr. C. W. Stiles, who kindly reported that he identified the worms as *Hymenolepis nana*, the eggs belonging to the same.

In Case 1, the large number of very young specimens found, the smallest being 3 x 0.15 mm., is noteworthy. The largest specimens were 15 mm. in length, the maximum width 0.6 mm. Senna, cited by Ransom,[2] noticed in feces containing *Hymenolepis nana* eggs many small rounded bodies measuring from 5 to 30 microns in diameter. The smaller of these were homogenous, with a thin membrane, while the larger were more granular and tended to become oval, with thicker membrane. Senna thought these might be eggs in the course of development which had prematurely escaped from the uterus, but finding similar bodies in two cases in which he could not demonstrate the presence of *Hymenolepis nana*, he was left in doubt as to their true nature. In Case 1, of this series, thirteen days after the second course of male fern and before the eggs had reappeared in the stools, there were found a large number of homogenous structures from 5 to 15 microns in diameter, bounded by a thin membrane. The next day, for the first time, *Hymenolepis nana* eggs were observed, with fewer of the smaller structures. These were not observed again.

SYMPTOMS

Of the seven cases four had definite symptoms, which, in the absence of other factors, may be attributed to the dwarf tapeworm. Two of the children had no symptoms and in both cases very few eggs were found. One patient with a heavy infection had long-standing headache, which may possibly have been due to the parasites. The most frequent symptoms were abdominal pain, or tenderness, and diarrhea, found in four cases. There were anemia, dizziness and headache in two cases, increased appetite in one case. The presence of blood in Case 1 is interesting. Innes, cited by Ransom, in reporting a necropsy on a case, states that he found bloody extravasations on the mucous membrane of the ileum, which may have been the points of attachment of the tapeworms lying free in the intestine.

Eosinophilia, according to Schloss[21] and others a constant finding in cases showing symptoms, ranged from 2 to 9 per cent. In the children with definite symptoms it was from 6 to 9 per cent., while in the others it was from 2 to 3 per cent.

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21. Schloss, O.: Arch. Pediat. **27**:100 (Feb.) 1910.

Treatment was instituted in three cases, and an apparent amelioration of symptoms occurred in all. Case 1, after four courses of treatment, still showed a few eggs in the stool on the day of the patient's discharge. Subsequently, after an attack of measles, his intestinal symptoms reappeared. In Case 4 apparently complete cure was obtained after one course of male fern. In Case 7 few eggs showed after one course of treatment.

MODE OF INFECTION

The development as well as the manner of infection of the dwarf tapeworm is unknown. There is a form of tapeworm common in rats, the *Hymenolepis murina* of Dujardin, which morphologically is very similar to *Hymenolepis nana*. Grassi,[2] quoted by Ransom, found this parasite common in rats in Catania, where also the dwarf tapeworm was common. In a series of carefully conducted experiments, he showed that the feeding of mature segments of *Hymenolepis murina* to rats was followed by infection with this tapeworm. The eggs liberate six-hooked embryos in the small intestine, which enter the villi of the last part of the ileum and there become transformed into cercocysts. The position of each cercocyst is in the dilated central lymphatic cavity of the villus. Subsequently, the cercocyst leaves its position in the villus and becomes changed to the adult worm, and is attached to the epithelium of the intestines. Just how the latter stage ensues is not noted. Joyeux[22] repeated these experiments successfully.

Grassi, Lutz and Ransom consider *Hymenolepis nana* of man identical with the rat hymenolepis, but Braun, Loos and others doubt this. Grassi, Loos, Stiles,[23] Schnell,[24] and Joyeux[25] were unable to transmit the infection to rats and mice. Stiles states that the "form from rodents is entitled to at least subspecific rank." Castellani[26] states that the dwarf tapeworm of man is probably distinct from the rat type.

Minchin and Nicholl, and later Johnston,[27] state that they found cysticercoids of *Hymenolepis murina* in the body cavity of *Xenopysylla cheopis* and *Ceratophyllus fasciatus,* but Joyeux states that he was unable to transmit the infection experimentally in these and other fleas.

Grassi fed worms and eggs of both types to eight indidivuals and in only one case were adult tapeworms found. In this case, a boy

22. Joyeux, C.: Bull. Soc. Path. Exot. **9**:578, 1916.
23. Stiles, C. W.: Osler's Modern Medicine **2**:252.
24. Schnell, W.: Centralbl. f. Bakteriol., Abt. **82**:304 (Nov. 11) 1918.
25. Joyeux, C.: Bull. Soc. Path. Exot. **12**:228 (May 14) 1919.
26. Castellani and Chalmers: Manual of Tropical Medicine, Ed. 3, p. 610.
27. Johnston, T. H.: Proc. Roy. Soc. Queensland **24**:63, 1913.

of 5 began to pass eggs fifteen days after ingesting several segments of the rat hymenolepis and later expelled·fifty worms on treatment. In another instance a boy who was previously free from *Hymenolepis nana* was infected after a month during which time he was collecting the feces of an infected patient. Grassi himself raises objections to these cases because of the high incidence of *Hymenolepis nana* in the locality and because worms may be present, although the stools are egg free.

The experiments of Grassi, together with the failure to find an intermediate host, have led to the assumption that the mode of infection is direct, and that man himself, like the rat, may be the intermediate host. Stiles accepts this possibility. As possible evidence of direct infection, Grassi cites cases of dwarf tapeworm infection in several individuals, previously egg free, in whose families there were known to be cases of *Hymenolepis nana*. Schloss[21] cites two similar cases in his series. The frequent findings of infection in several members of the same household would also point to the possibility of a direct infection. Thus the Hygienic Laboratory staff[28] found five cases in the same ward on an insane asylum. Magnenat, quoted by Stiles,[1] reported four cases in the same family. In all but one of Schloss' cases several members of the same family were infected. Carpenter,[29] in discussing DeBuys' paper before the American Pediatric Society, described an epidemic of *Hymenolepis nana* in a foundling asylum in Philadelphia and thinks the infection was direct. Rats examined by him were negative.

I attempted to determine the mode of infection of the dwarf tapeworm. The feeding of eggs and mature segments to six rats and six mice was negative. Attempts to incubate the eggs following their mixture with artificial gastric juice were also negative.

The house of family B was carefully inspected and found to be in a very unsanitary condition. The children played around the floor a great deal so that chances for coprophagia were very favorable. There were no rats. Several bedbugs were examined and were negative for cysticerci. Several lice from the head of Case 4 were also negative.

There was an old pet dog with which the children were very intimate. A stool from the dog, obtained while the dog was at the B. home, showed several eggs, which were exactly similar to eggs of *Hymenolepis nana,* the characteristic filaments of the latter being present. There were also present trichomonads and eggs of *Dipylidium caninum* and *Tenia serrata*. The dog was removed from the

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28. Stiles and Garrison: U. S. P. H. S., Hyg. Lab. Bull. **28:** 1906.
29. Carpenter, H. C.: Arch. Pediat. **36:**379 (June) 1919.

home and daily examinations of stools were made, but hymenolepis eggs could no longer be found. Two weeks later a necropsy was made and *Dipylidium caninum* and *Tenia serrata,* but no *Hymenolepis nana* were recovered.

The presence of the parasite in all but the oldest boy, age 12, is of interest. In Case 5, no eggs were observed in the specimen of February 22 after twelve examinations, while on March 27 the stool was loaded with them. The difficulty of ridding the host of all the worms is a striking feature. It has been stated by Ransom and other authors that one course of treatment is frequently not sufficient. In two of my three cases which were treated eggs showed subsequently. In Case
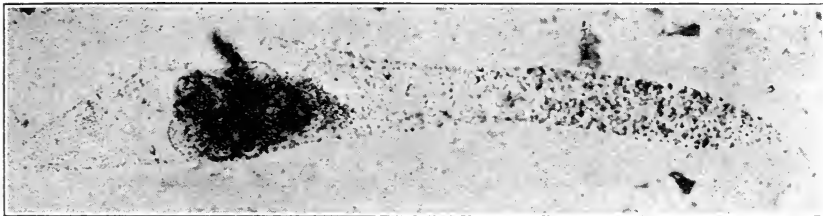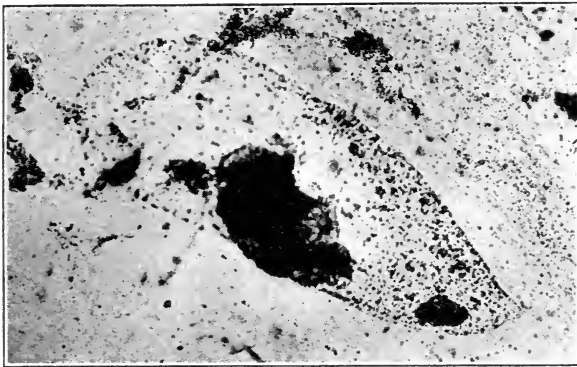
Figs. 1 and 2.—Head of dwarf tapeworm surrounded by saclike structure. Head shows some details.

1 four courses of treatment were given and at the end of these there were still many eggs present. The large number of very young forms following the second treatment was striking.

Following the last administration of the vermifuge, the full dose being repeated next day because of the vomiting of the male fern, there were passed a number of mucoid looking tags of tissue, but no worms. The largest of these pieces were 20 x 10 mm. Each had from two to eight heads of *Hymenolepis nana* studded throughout it, but no segments could be found. Microscopically, there were observed the rostellum, a row of hooklets, four suckers and a small caudal append-

age.   Surrounding each head there could be seen in the unstained specimen a definitely clear area.   In the stained specimen, there was seen microscopically a saclike structure completely surrounding each head.   The shape of the structures varied, some being elliptical, others ovoid, still others approaching a spherical shape.   Grossly, both the head and the sac could be seen in the stained tissue.   It does not seem likely that the adult worm could develop within the saclike structure.

Figures 1 and 2 show the relative size and shape of the head and sac. The tissues were stained several times with hematoxylin-eosin and also with methylene blue, but no nuclei could be seen.   I felt that the structures might possibly represent the cercocyst stage of the dwarf tapeworm, thus indicating that man himself may be the intermediate host.   The occurrence of autoinfection is proved by the large number of worms present and the difficulty in getting completely rid of them.

SUMMARY

1. A review of the literature shows that the dwarf tapeworm is the most common tapeworm in many parts of the United States.

2. The first cases of *Hymenolepis nana* from St. Louis are reported.

3. A possible cercocyst stage of *Hymenolepis nana* is demonstrated in man.

BLOOD PRESSURE IN UNIVERSITY FRESHMEN AND OFFICE PATIENTS [*]

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SAN FRANCISCO

What is the average blood pressure for a man or woman of a given age? How common is hypertension in young people? What is its significance, particularly in early life? These are some of the questions which occurred to me after taking the blood pressures on 265 men called in the closing days of the second draft.[1] Although clinical experience had led me to expect a high incidence of hypertension in young men, it had not prepared me for the finding that in this particular series there were more with pressures over 130 mm. than under; and very many with pressures between 160 and 275. It was soon clear that this group did not represent a fair sampling from the community because so many were rejects from the recruiting offices; that is, most of the physically fit had gone to war and the unfit were left.

On turning to the available statistics, it was surprising to see that most of them must be objected to on this same score of previous selection. Thus Smith[2] studied 500 aviation recruits, Sorapure[3] 796 soldiers, Goepp[4] 9,996 accepted insurance cases, Fisher[5] 12,647 accepted insurance cases, MacKenzie[6] 31,934 accepted insurance cases, and Woley[7] 1,000 insurance cases which remained after excluding those with histories or physical findings suggestive of cardiovascular abnormality. The insurance statistics would have much more value if they were based on the examination of all applicants; but even then

1. Alvarez: California State J. M. **17**:367, 1919.
2. Smith, B.: J. A. M. A. **71**:171 (July 20) 1918.
3. Sorapure: Lancet **2**:841, 1918.
4. Goepp: Penn. M. J. **22**: 295, 1919.
5. Fisher: Proc. Assoc. Life Ins. Med. Directors of America, N. Y., 394, 1912; 90 and 246, 1915; 203, 1917.
6. MacKenzie: Ibid, 221, 1917.
7. Woley: J. A. M. A. **55**:121 (July 5) 1910.

there would undoubtedly be a considerable amount of adverse selection because those with hypertension often have premonitions of future illness; and many seek insurance after discovering their defects.

The next question then is: how are we to get a fair sampling? An ideal way would be to examine every tenth individual passing a certain point on a busy street. Different strata of society might be sampled by choosing streets in different parts of the city and also by choosing different cities. Unfortunately, such methods are not practicable at present. The next best thing probably would be to study the young people gathered together in the public schools and colleges. Particularly in state universities where tuition is free it would seem that the student body should represent a fair sampling from the more intelligent part of the community. Fortunately, it is becoming more and more the custom in the leading schools to examine the incoming freshmen. Lee[8] and Barach and Marks[9] have already reported on the blood pressure readings in some 1,200 college students, but their groups were not large enough for analysis by age and sex.

During the last few years all the freshmen entering the University of California have been subjected to a physical examination which includes the measurement of the blood pressure. Under ordinary conditions this mass of data which has accumulated at the university infirmary would have been ideal for my purposes. Unfortunately, however, the war with its demands on the fittest of the young men, has made me uncertain of the sampling even in the ages below 21. In 1918 most of the men were gone; but some were enrolled in the S. A. T. C., and some probably remained on account of physical handicaps which turned them back from the recruiting offices. Certain it is that there is a big difference between the average pressures of the male entrants in 1919 and the pressures of those in the three preceding years. As would be expected, there is practically no difference in the figures for the corresponding groups of women (Fig. 5). I hope to clear up these uncertainties by getting more and better data in the next few years.

TECHNIC

Unfortunately, the methods of taking the pressures are not exactly the same for men and women. The men take a tepid shower before the examination and are then examined in the reclining position. They are more likely to stand around in negligé and get cold than are the women. The women's pressures are taken standing. The systolic pressure, the only one studied at this time, was taken by palpation. This is the more reliable method as it is less subject to wide variations.

8. Lee: Boston M. & S. J. **173**:541, 1915.
9. Barach and Marks: Arch. Int. Med. **13**:648 (May) 1914.

One aneroid (a large Tycos) and three mercury column instruments were used. The aneroid was checked at regular intervals against a mercury column. The records were taken off the cards and arranged as in Tables 1 and 2. This shows, first, that the data on the women are much better for statistical purposes than those on the men because the women examiners have read quite closely to the millimeter, while the men have had a strong tendency to read to the nearest multiple of ten. For practical purposes, and especially when measuring a value that often fluctuates from hour to hour, it is of little importance whether a pressure is 150 or 160 mm., but for statistical work and especially for drawing curves of frequency distribution, it is much better to have the data evenly distributed. It is useless to try and make the steps less than 2 mm. because that is the unit on most of the scales.

A glance at Table 1 shows that the lowest age is 16. There were 99 women and 34 men who entered the university at that age during the period covered. Three thousand, three hundred and thirty-three (3,333) entered between the ages of 18 and 19. The curves of frequency distribution for the different ages for the two sexes are shown in Figure 1. The abscissae represent the blood pressures by 5 mm. Stages. In these units " 85" $=$ 85 to 89, and "90" $=$ 90 to 94. When 85 is made to include from 83 to 87 the only difference in the curves is one due to the exaggeration of the deformity brought about by the grouping of the data about the multiple of ten. The ordinates represent percentages at the different pressures.

A study of these curves shows several interesting things. In the first place, as Kilgore[10] has pointed out, they are fairly symmetrical and correspond to the type "A" curve so well known to statisticians. It is the curve obtained when we chart the heights of a thousand men, the errors in 100 measurements of a meter bar, or the results of a thousand throws of dice. In all these studies of large groups of observation it has been found that most of the data will lie more or less closely about the average. Hence it is that the probability that small errors or deviations from the average will occur is larger than the probability that large errors or deviations will occur. Thus, in measuring a thousand men with an average height of 5 feet 6 inches, the probability of finding men 5 feet 5 inches, and 5 feet 7 inches in height is much greater than the probability of finding men 5 feet or 6 feet tall. There will be scores of the former to one or two of the latter. With the help of mathematical formulae we can calculate just how many of the data are likely to fall within certain limits measured on each side of the average. The divergences between the calculated

10. Kilgore: Lancet **2**:236, 1918.

and the actual curves are often very slight as will be noted in Figures 2 and 3. A study of the differences which do appear is sometimes very helpful.

The simplest and shortest way in which to compare the curves is to plot the data on paper which has been ruled according to the theory of probability, with small spaces near the 50 per cent. mark and wide ones near the 0.01 and 99.99 per cent. marks. If the data follow the theory, they will plot out in a straight line. Those who have difficulty in following this part of the discussion would be much helped by reading Whipple's [11] and Rugg's [12] little books on applied statistics.

Figure 3 shows the data for 5,807 women and 2,930 men plotted on probability paper. It will be noted that the figures for the women between pressures of 110 and 130 lie along a straight line; as do those for the men between 90 and 140 mm. This suggests strongly that within those limits deviations from the average are due to various small errors subject to the law of chance. Deviations above and below these limits are probably due to pathologic factors. It will be noted also that the line for the women is more nearly vertical than that for the men. This demonstrates a fact which will be shown again later in other ways, and that is that the dispersion is less for the women: i. e., their readings are grouped more closely about the average. This is well shown in Figure 2 where we can compare the distribution curve for the women with that for the men. The women's curve is high and narrow; the men's is low and wide. The average for the women is 115 mm.; for the men 126.5 mm. If we get the average of the deviations from the average we find that for the women it is 8.0 mm., and for the men 10.8 mm. In Figure 2 the distribution curves have been smoothed so as to remove the humps which are seen in Figure 4. This smoothing is done by averaging the values of different points on the curve with the values of the two adjacent points (Rugg,[12] p. 184). The solid lines represent these smoothed curves. The lines of dots and dashes represent the probable curves secured by plotting the intersections of the two straight lines drawn through the data in Figure 3. The dotted lines represent the theoretical curves obtained mathematically, using the so-called standard deviation which for the women is 2.12 (of the 5 mm. abscissae units) and for the men, 2.98. Given these data it is easy to calculate the values of the ordinates corresponding to the different abscissae. The results of the graphic and mathematical methods are so close for the women that only one theoretical curve has been plotted.

11. Whipple: Vital Statistics, N. Y., 1919.
12. Rugg: Statistical Methods Applied to Education, Boston, 1917.

TABLE 1.—BLOOD PRESSURE OBSERVATIONS ON WOMEN STUDENTS

Pressure	Ages													Total	Percentage		Theoretical Percentage from Probability Paper		Theoretical Percentage Computed from Standard Deviation	Smoothed Curve in Percentages
	16	17	18	19	20	21	22	23	24	25 to 26	27 to 30	31 to 35	36 to 40							
80-84	1		2			1								4	0.07	0.07	0.10	0.10	0.07	0.07
85-89			2	3	1	2								14	0.24	0.31	0.42	0.32	0.34	0.24
90-94	1	1	8	9	5	1	2	1	1	2				32	0.55	0.86	1.70	1.28	1.13	0.55
95-99	4	13	34	23	12	13	12	3	1	7	2	7	7	157	2.70	3.56	5.00	3.30	3.20	2.70
100-104	4	34	111	83	48	39	36	7	8	33	1	7	19	514	8.85	12.41	11.50	6.50	7.00	8.85
105-109	19	62	104	110	64	55	38	28	14	27	10	24	14	633	10.90	23.31	23.00	11.50	12.30	12.00
110-114	14	95	281	223	118	122	61	31	18	61	41	35	25	1,247	21.50	44.81	40.00	17.00	17.00	16.90
115-119	12	74	161	145	109	82	40	49	56	49	56	67	21	879	15.12	59.93	59.00	19.00	18.90	18.30
120-124	20	94	221	188	103	97	60	47	40	52	75	45	23	1,058	18.20	78.13	76.30	17.30	17.00	15.40
125-129	12	65	135	108	54	39	26	45	26	18	54	57	12	578	9.80	87.93	87.90	11.60	12.20	10.90
130-134	5	45	89	63	41	31	24	27	16	18	72	19	11	403	6.94	94.87	95.00	7.10	7.00	6.94
135-139	6	15	36	30	14	13	10	11	16	5	37	22	6	157	2.70	97.57	98.30	3.30	3.30	2.70
140-144	1	10	22	17	7	3	7	3	3	2	27	12	1	92	1.59	99.16	99.55	1.25	1.13	1.59
145-149		3	3	7	2	4	1		1		5	2	4	24	0.41	99.57	99.90	0.35	0.34	0.41
150-154		1		3	1	1		3	1		1	1		17	0.29	99.86	99.98	0.08	0.07	0.29
155-159			1	1						1	2		1	4	0.07	99.93				0.07
160-164			1							2				2	0.03	99.96				0.03
165-169			1											2	0.03	99.99				0.03
Total....	99	512	1,214	1,014	579	503	317	259	201	277	383	302	150	5,807						
Average...	115.8	117.2	116.5	116.2	116.2	115.7	116.5	115.4	115.4	114.7	115.4	117.3	118.3	115.0						

Average deviation of the 5,807 = 1.6 × 5 = 8 mm.
Standard deviation = 2.12 × 5 = 10.6 mm.

Coefficient of variation $\dfrac{100 \times \text{S.D.}}{M} = \dfrac{212}{115} = 1.85$

TABLE 2.—BLOOD PRESSURE OBSERVATIONS ON MEN STUDENTS

Pressure	Ages													Total	Percentage		Theoretical Percentage from Probability Paper		Theoretical Percentage Computed from Standard Deviation	Smoothed Curve in Percentages
	16	17	18	19	20	21	22	23	24	25 to 26	27 to 30	31 to 35	36 to 40							
80–84	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
85–89	..	1	3	..	..	..	..	..	..	..	..	..	..	3	0.10	0.10	0.06	0.06	0.30	0.10
90–94	..	1	3	3	1	..	..	..	..	..	..	..	..	13	0.44	0.54	0.20	0.14	0.70	0.21
95–99	1	1	3	11	3	4	1	..	..	..	3	..	..	34	1.16	1.70	0.60	0.40	1.49	1.33
100–104	..	1	13	17	11	10	..	..	..	2	..	1	..	77	2.62	4.32	1.70	1.10	2.81	2.10
105–109	2	2	13	11	13	11	..	..	..	2	..	1	..	69	2.35	6.67	4.00	2.30	4.78	3.75
110–114	4	13	35	41	27	7	9	2	3	..	5	2	9	199	6.80	13.47	8.00	4.00	7.38	7.16
115–119	9	21	53	54	42	14	5	3	3	12	2	2	2	321	10.95	24.42	15.50	7.50	10.00	11.78
120–124	4	30	107	91	59	35	19	14	8	18	8	11	6	505	17.23	41.65	26.00	10.50	12.32	13.77
125–129	9	24	63	80	33	64	30	19	13	21	19	9	2	361	12.32	53.97	39.50	13.50	13.46	14.39
130–134	4	29	99	83	70	43	40	31	15	20	23	8	6	500	17.10	71.07	54.00	14.50	13.18	13.34
135–139	6	35	48	48	26	55	27	34	14	34	16	15	6	251	8.57	79.64	68.00	14.00	11.50	10.26
140–144	2	23	40	48	40	30	38	30	19	9	13	7	5	261	8.91	88.55	80.00	12.00	9.00	7.49
145–149	3	15	24	17	13	24	17	11	10	6	3	3	..	97	3.30	91.85	88.50	8.50	6.26	4.83
150–154	1	5	24	29	8	6	22	20	13	2	3	3	1	109	3.71	95.56	94.40	5.99	3.88	3.41
155–159	..	7	16	8	7	13	7	..	5	4	..	..	..	50	1.71	97.27	97.40	3.00	2.15	2.25
160–164	1	1	11	..	3	6	9	5	7	1	..	2	1	48	1.64	98.91	99.00	1.60	1.07	1.46
165–169	..	2	3	1	3	4	4	..	1	5	4	1	..	14	0.48	99.39	99.55	0.55	0.36	0.76
170–174	..	1	4	1	3	3	5	1	3	1	..	..	..	10	0.34	99.73	99.90	0.45	0.15	0.43
175–179	..	..	1	..	..	1	..	1	..	2	1	..	..	6	0.20	99.93	99.96	0.06	....	0.23
180	..	..	..	..	..	..	..	2	..	..	..	..	..	2	0.06	99.99	99.99	0.03	....	0.07
Total.....	34	212	560	545	362	330	233	178	113	139	117	66	40	2,930						
Average....	126.3	128.2	127.8	126.2	126.3	125.4	126.2	126.3	130.0	126.9	126.0	126.8	....	126.5						

Average deviation of the 2,930 = 2.17 × 5 = 10.85 mm.
Standard deviation = 2.98 × 5 = 14.90 mm.

$$\text{Coefficient of variation} \quad \frac{100 \times \text{S.D.}}{M} = \frac{298}{126.5} = 2.35$$

A glance at these curves shows that the agreement between the found and the theoretical data is close. The main difference is that the actual curves drop off a little too rapidly at first on the upper side and then later they do not drop off fast enough. This deformity of the curves suggests strongly that the figures over 137 mm. for the women and over 148 mm. for the men represent pathologic conditions. If we turn again to Figure 3, we see that according to the theory of probabilities only one man in 10,000 should have a pressure over 175. Actually there were eight in 2,930 or twenty-seven in 10,000. Similarly, there should have been only one woman in 10,000 with a pressure over 150; actually there were twenty-five in 5,807 or 43 in 10,000.

The higher figures are modified by the incidence of hypertension; the lower ones by fainting and perhaps by convalescence from acute infections. I threw out a number of records below 90 mm. on which fainting was definitely noted, but it is likely that many of the low records included might also have been removed for this reason. To be entirely consistent, I should probably have left these records in, just as I have left in the high records in cases where excitement may have been a disturbing factor.

In Figure 1 it will be noted that the modes or apices of the men's curves lie between 120 and 130; those of the women lie between 110 and 120. This difference of 10 mm. between the pressures of the two sexes has been noted by previous observers. It is remarkable that there is practically no change in the location of the mode between the ages of 18 and 40. That for the men is actually a little lower at 33 than at 17; and that for the women is lower at 38 than at 16.

There are some differences in the frequency polygons for the various age groups, but owing to inaccuracies in the readings, to the smallness of some of the groups and to uncertainties about the sampling we cannot lay much stress on them. The sexual difference is most marked at the age of 24. It is suggestive that the curve for the 16 year old boys resembles that for the women; and that for the women over 36 resembles that for the men. The possible significance of this finding will be discussed later.

THE AVERAGE BLOOD PRESSURE

Figure 4 shows the arithmetical means (averages) of the different age groups plotted on coordinate paper. It will be seen that the curve of average pressure not only does not rise steadily as it has been supposed to do, but actually drops from 17 to 25 in the women and from 17 to 21 in the men. This finding was so unexpected that every care has been taken to insure the accuracy of the figures. Ordinarily, such averages are obtained by grouping the data and then applying

short-cut methods.   In this case no grouping was done, and the figures charted represent the means of the actual data as they were taken off the records.   As there was considerable doubt about the reliability of the sampling in the men's group, I divided the data into two parts: those obtained in 1919, and those obtained before that.   Figure 5 shows the average for the two groups separately and combined.   Many of the ages are not represented because the number of readings was too small.   In order to save time these averages were computed by the short-cut method.   The dotted line is that of the more exact averages shown in Figure 4.   These curves show the reliability of the sampling for the women.   The 1919 women (between 17 and 22) average about 1.0 mm. higher than do those for the preceding years. This difference is so small and so consistent that it may be due to the personal equation of the examiners or to errors in their instruments. The trend of the average in both groups of women is downward during these years.

When we turn to the curves for the men we find differences so large that it would seem that they must be due to disturbances in the sampling.   This difference ranges from 9 mm. at 18, to 3.5 mm. at 23; the 1919 men showing the higher figures.   The average of the 1919 men falls from 18 to 23, while that of the pre-nineteen men rises from 18 to 24.   No significance can be attached to the big rise in the combined average at 24 because it is not present in the pre-nineteen curve, unless it be that the rise at 23 there corresponds to the rise at 24 in the 1919 curve.   It is hard to explain the big differences in the men's curves as we do not know enough about the ways in which the sampling was modified.   Some might perhaps ascribe the increase in average pressure in 1919 to the strain of the War year, but that seems to me improbable.

There is little doubt about the drop from 17 to 25 in the women's curve as it appears in both the 1919 and the preceding groups.   It appears also in the curve drawn from data secured on 1,000 of my office patients.   This drop does not seem to have been described heretofore.   The most extensive studies of the yearly average have been made by MacKenzie [6] and Fisher.[5]   Their figures, for men only, when plotted on coordinate paper, lie in a practically straight line from 119 mm. at 17 to 140 mm. at 66.   Unfortunately, these observations have little value to us; the line had to be straight because only those men were accepted who varied within prescribed limits from a prescribed standard.

After 25, the average curve for the women rises rapidly.   In the series of office patients it was found to rise so much more rapidly than that for the men that it crossed over about the age of 40.   After
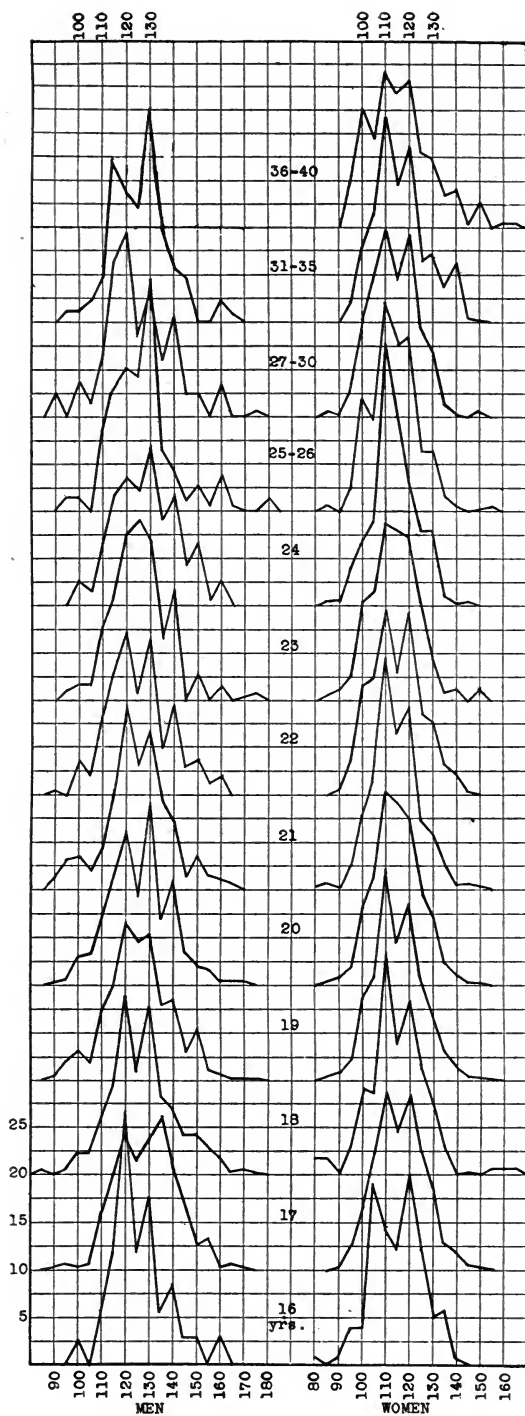
Fig. 1.—Frequency distribution curves for men and women students at different ages. The abscissae are pressures in mm. and the ordinates are percentages. In order to shorten the chart the ordinates for different age groups are made to overlap.

that the women averaged higher than the men (Fig. 6.). What we need now is more information about the trend of these average curves below 17 and above 35. We must know where the sexual difference appears and when it disappears or becomes reversed. Work is now being done on this problem in the children's clinic at the Universities of California and Stanford.

Another feature of the frequency distribution curves in Figure 1 which requires comment is their apparent bimodality, i. e., their tendency to show two peaks. Exceptions are found in the men at 16, 19, 23, 24 and 25, and in the women at 20, 23, 24, 25 and 36. This peculiarity is due in most instances to the tendency of the examiners to read to the nearest multiple of 10 on the scale. That tendency, however, will not explain the bimodality of the men's curves at 17 and 31,

Theoretical curve computed from Standard Deviation `- - - - - - - -`
      "   "   "   " probability paper `—— · —— · ——`
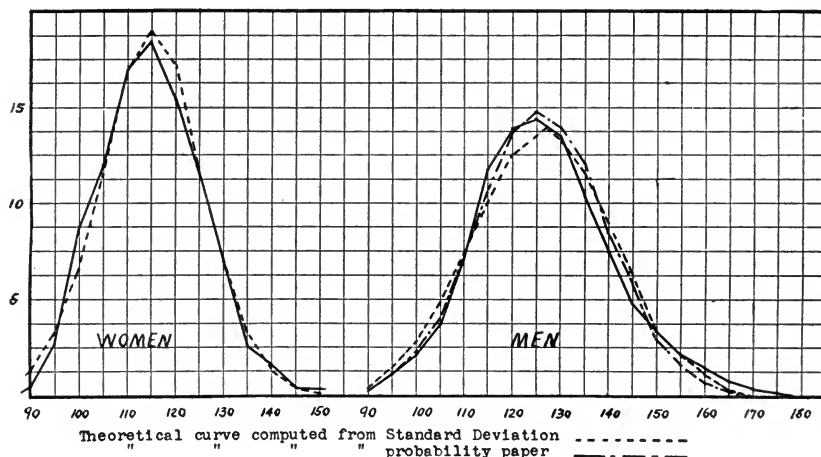
Fig. 2.—The solid lines represent smoothed frequency curves for 5,807 women and 2,930 men students from 16 to 40 years of age. The dotted lines represent the corresponding theoretical curves computed mathematically. The dash and dot lines represent theoretical curves obtained by plotting the straight lines in Figure 3. The ordinates are percentages and the abscissae, pressures.

and of the women's curve for 16, where modes fall on 105, 115, and 135 mm. Particularly in the case of the women, where the readings were made with great care, it is hard to understand why the sides of the graph should show so little evidence of deformity when the top is deeply notched. If we could be sure of the figures, the bimodality of the curves might lend support to my theory that there are perhaps two types or varieties of the human species: one in which hypertension will not develop, except perhaps in old age; and the other in which it, or allied disturbances, develop early on the basis of a congenital predisposition. Unfortunately for this argument, even when there

are two groups, if their modes are close together the fused curve will be unimodal. This is shown in Figure 7, where the solid line represents the distribution curve for all the women and men, taken together. Here we see how two groups with different modes can fuse so that
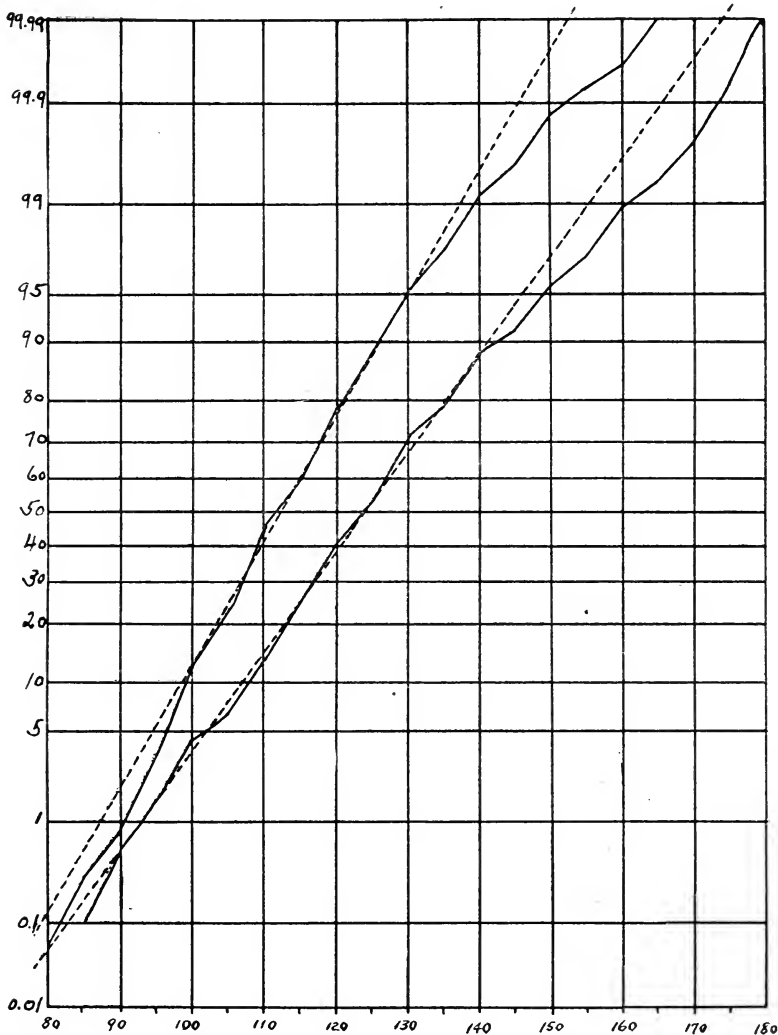
Fig. 3.—Shows the data for men and women students plotted on probability paper. The ordinates represent percentages; the abscissae, pressures. If the observations followed the law of probability exactly they would plot as a straight line.

the resultant curve is similar in form to the individual ones. If there had been equal numbers of men and women in the two groups the combined curve would have been like that in the corner of Figure 7.

That curve, with its mode at 120, probably comes pretty close to representing the distribution of blood pressures in Americans between 16 and 36.

DISCUSSION

Before entering on a discussion of the findings it might be well first to answer an objection which has been made by many of the friends who have seen these data during the last year, and which may be made again. These men felt that the higher figures should be disregarded because it is well known that the pressure in some people varies from hour to hour, and that it often goes up under excitment.[13]
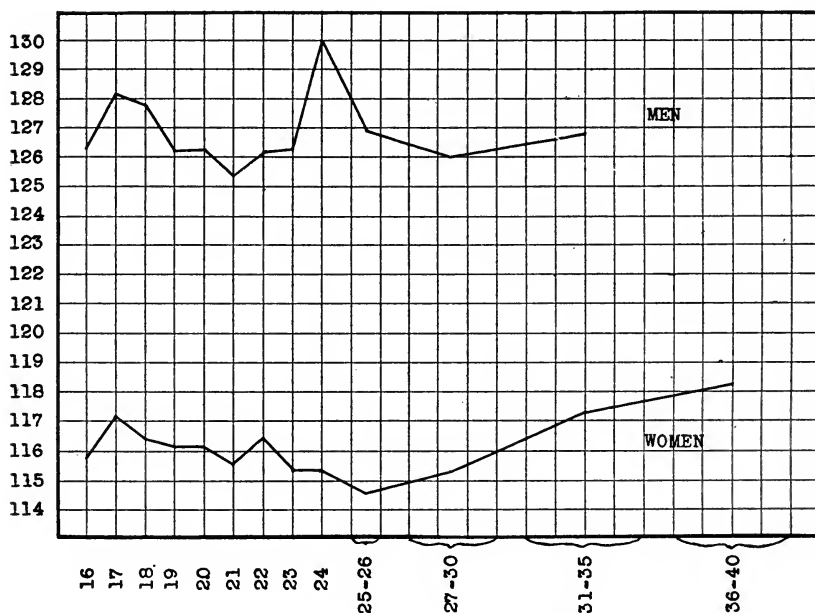
Fig. 4.—Shows the curves of average pressure for men and women between the ages of 16 and 40.

While this is true, it must be remembered that all the students were examined in the same way so that all were equally subject to excitement; and yet one developed a pressure of 115 mm., another 155, and another a fainting spell with a pressure of 80. By examining the men with 155 and 80, day after day, we might, perhaps, get figures more nearly in accord with our ideas of what they should be, but such juggling of disturbing data is not permissible in a scientific study. If we are going to measure some over again we must measure them

13. O'Hare: Am. J. M. Sc. **159**:369, 1920.

all. On another day some of the high pressures would undoubtedly be lower, but some of the borderline ones and some even of the high ones would be found higher.

Unfortunately, I have not been able to measure these students over again, but I have taken a series of carefully recorded measure-
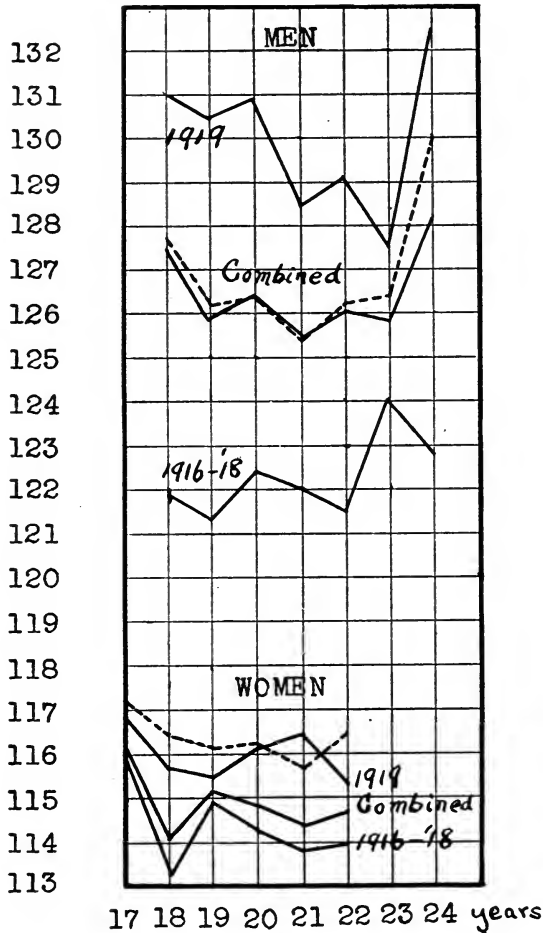
Fig. 5.—Showing differences in the averages in the different age groups, for 1919 and for 1916-1918. The ordinates are pressures and the abscissae, ages. The middle lines show averages for the combined data of 1916-1919. These averages were obtained after grouping the data by stages of 5 mm. The dotted lines are exact averages taken from Figure 4.

ment on 100 consecutive office patients, 50 women and 50 men, who were observed twice at varying intervals of time. In spite of the fact that many of these people took treatment: rest cures, etc., in the interims between the two measurements; and in spite of wide individual

variations, there was a difference of only 0.07 mm. between the first average and the second. On the second examination, the women averaged 1.94 lower, while the men averaged 2.08 mm. higher. These findings make me feel that if I could measure the students over and over again with great care, individual variations would probably balance each other so that the frequency polygons and averages would remain about the same. Furthermore, it must be remembered that not only can the excitement account for an increase in pressure but a tendency to hypertension will often account for the excitement. The phlegmatic individual with a normal pressure is perhaps bored by the proceeding, while the keen hypochondriac with an over sensitive
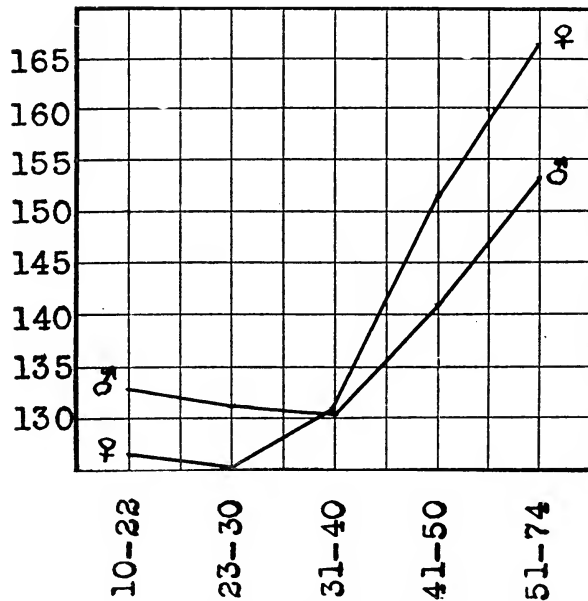
Fig. 6.—Shows yearly averages on 1,000 office patients. The abscissae represent age groups. The curve for the women is below that for the men before 40, and above it afterwards.

and erratic vasomotor system is afraid that serious organic lesions will be found; he gets nervous and his pressure goes up. It is not improbable also that it is the man with the hypertensive diathesis who is most likely to show the wide variations. One of the characteristic things about these people is their vasomotor instability; they blush, they blanch, they feel hot in one part of the body and cold in another. There is good reason, therefore, for expecting their blood pressures to be more variable than those of the people with good vasomotor control. Furthermore, we probably get a much better idea about a man's vasomotors and his blood pressure when he is under a little strain than

when he is under the most favorable conditions, just as we can judge better about a man's heart after exercise; about his pancreas after feeding sugar, and about his kidneys after feeding salt or urea. At any rate, the essential point is that if a thousand young people are examined on one day under the same conditions, with the same instruments and the same examiners, some will be found with low pressures, many with medium ones and a considerable number with high ones.

The next thing to do before we can discuss the incidence of hypertension in these students is to define the limits of normal. Such a
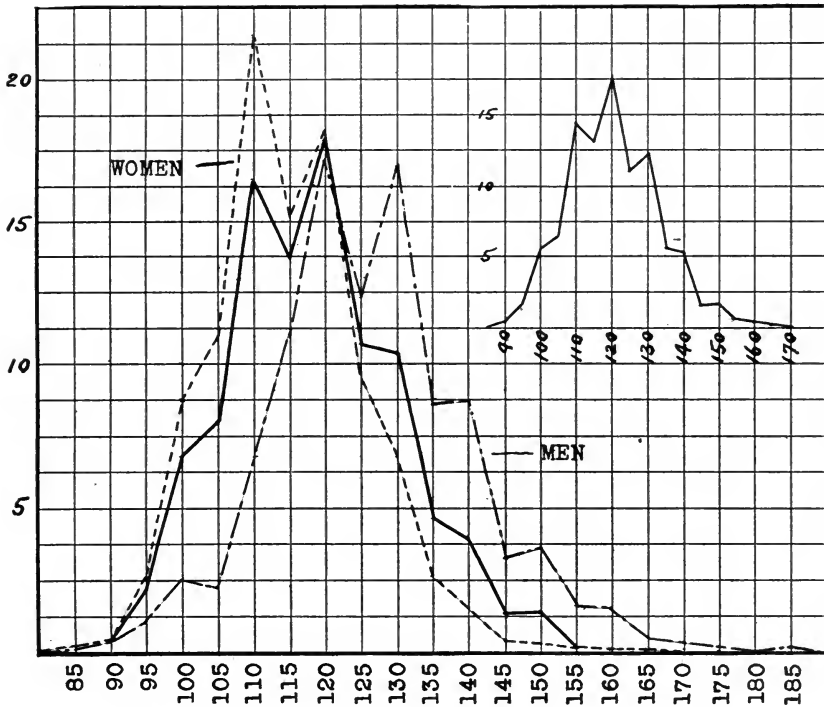
Fig. 7.—To show that a unimodal curve can conceal the fact that there are two groups present with modes at 115 and 125 mm. The solid line represents the distribution for 8,737 men and women together. The small curve in the corner shows this distribution as it would have been if there had been equal numbers of men and women.

definition will be of interest not only to the student but to the clinician and to the life insurance medical director. There are several ways in which we can approach this problem. We can find the average and take certain limits on each side of it; we can study the points of divergence of the actual from the theoretical frequency curve, and best of all, we can watch a large series of borderline cases to see which

ones have, or later develop, other signs of cardiovascular-renal peculiarity.

The arithmetical mean for the men is 126.5; for the women 115.0 mm. If we exclude the data below 100 and above 130 we get 120.3 for the men and 114.4 for the women. Figure 3 shows that the median or mid number of the men is 123.5; for the women it is 112.5. The median is often a good measure of central tendency because it is not so much affected by the widely divergent figures as is the mean. Mathematicians often estimate the "probable error" or limits within which the middle 50 per cent. of the data will lie. For the men these limits are 115-132.5 for the median and 116.5-136.5 for the mean. For the women the limits are 105-119 for the median and 107.8-122 for the mean. Judging by clinical experience, these figures do not seem to be very helpful. They suggest that the measures of central tendency are placed too high for the men. They show again very clearly the great difference in the dispersion of the data for men and women.

If we turn to Figure 3 we note that the data for the women follow the law of probability between limits of 100 and 130 mm.; the data for the men follow the law between 90 and 140 mm. That suggests strongly that between these limits variations from the average are due to many small errors attendant on the method of measurement, the condition of the subject, etc. Above and below these limits the divergence of the found from the expected would appear to be due to pathologic causes. This is shown still more clearly in the curves from office patients. See figure 8. In these, there can be no doubt but that the humps off to the right, in some instances entirely separate from the main polygon, represent pathologic cases.

Let us turn now to the limits which have been set by various writers in the past. One often hears it stated that the pressure for any age is roughly 100 plus the age. Figure 4 shows at a glance that that rule cannot be used in youth when the pressure is declining with age. The life insurance statistics show that it cannot be used even for older men. According to MacKenzie, the normal range for men between 15 and 39 is 26 mm. Taking our mean of 126.5, the limits would be 113.5 and 139.5. Fisher thinks 12 mm. above the average for the age is a permissible deviation. For the women this would make 127 the upper limit. Janeway [14] was inclined at first to take 150 or 160 mm. as the upper limit of normal, but in 1915 [15] he said, "I am inclined to revise my former opinion and to agree with Cook and Lauder Brunton before him that over 135 mm. up to middle life,

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14. Janeway: Arch. Int. Med. **12**:755 (Dec.) 1913.
15. Janeway: Bull. Johns Hopkins Hosp. **26**:341, 1915.
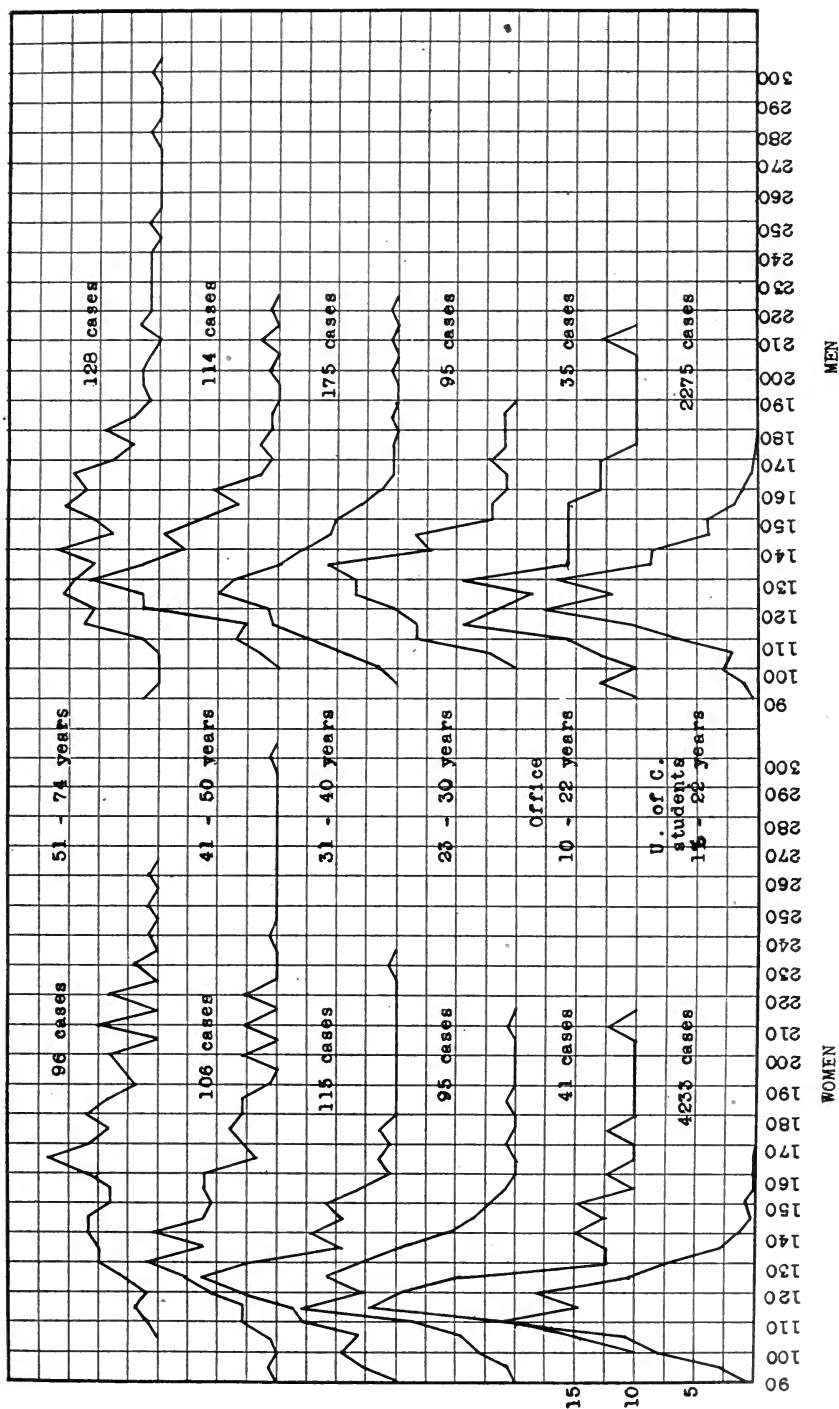
Fig. 8.—To show frequency distribution of blood pressures in 1,000 office patients at different ages, compared with the distribution of 6,508 students between 16 and 22. The changes in the women's curve after 40 is well shown.

and 145 to 150 mm. thereafter should be regarded as pathologic hypertension if found on repeated examinations." In a series of 7,872 office patients, he found 11.1 per cent. with pressures of 165 mm. or over. Lee,[8] who studied Harvard freshmen, places the upper limit at 140 mm. In his series of cases he had 12.8 per cent. exceeding that figure; at the University of California there were 20.4 per cent.

It seems pretty clear from a study of the literature that with the passage of time and the accumulation of knowledge about the subject, the tendency is to lower the upper limit of normal. A few years ago I would have accepted 135 or 140 mm. as the upper limit of normal for young people, but I have seen so many men and women in whom pressures between 130 and 135 were associated with irritable, enlarged hearts, anginoid pain, dizziness, morning headache, cyanotic hands, transient albuminuria and other typical findings, that we feel that the upper limit for the men should be placed at 130. Theoretically the limit for the women should be 5 or 10 points lower, but practically it would seem to be a little higher, perhaps about 127. This may be because women often appear to tolerate hypertension better than the men do.

TABLE 3.—Percentages Including and Over the Different Pressures in the California Students; in the Students Studied by Barach and Marks, and by Lee (See Bibliography); in One Thousand Office Patients, and Thirteen Thousand Seven Hundred and Eighty-Nine Middle Aged Men Applying for Insurance

Blood Pres- sure, Mm.	Univ. of California Students			Barach and Marks, 18-31 Years	Lee	Office Patients, 10-40 Years		13,789 Insurance Appli- cants, Men
	Men		Women			Men	Women	
	1916-1919	1916-1918	1916-1919					
130	46.0	36.0	12.0	47.0	....	53.0	38.0	
135	28.9	....	5.1					
140	20.4	12.0	2.4	24.0	12.8	26.0	21.0	
145	11.5	....	0.8					
150	5.6	4.7	0.4	9.4	....	14.0	12.0	9.0

According to Table 3, the 130 mm. limit seems reasonable enough so far as the women students are concerned; but it seems as if it must be too low for the men. It may be, of course, that the sampling was bad, and that in later years we will get figures even lower than those obtained in the years before 1919. It is interesting to see how much more frequently hypertension is found in women who go to a doctor's office than in women who go to college. The difference is not so marked for the men. At first sight these figures may seem incredible, but let us check them in several ways. At the office I have found that practically all of the men with pressures over 130 show other signs of cardio-vascular peculiarity. The insurance exam-

iners say that 83 per cent. of the applicants with pressures over 150 can be rejected for albuminuria, cardiac hypertrophy, etc. (1917, p. 252). Table 2 in my article on drafted men shows how rapidly the percentage of such abnormalities rises with the increase of blood pressure: from 54 per cent. at 130 mm. to 100 per cent. at 166 mm. Lee found other cardiovascular troubles in twenty-two out of the eighty-five students with pressures over 140 mm. In this group of 662, 5.1 per cent. had albuminuria. MacLean[16] who studied 60,000 soldiers (already selected) found albuminuria in 12.6 per cent. after exercise. Unfortunately, the statistics of the provost marshall general on the draft do not help us much because so many of the men did not have a complete examination, but were dismissed as soon as some obvious disqualification such as an amputation, a stiff joint or a large hernia became apparent. Moreover, the work was done hurriedly; blood pressures were rarely taken and analyses of the urine were rarely made. In 1917, 2,521 of those passed into the army had almost immediately to be treated for valvular heart disease.[17] Even among the carefully picked aviators, Whitney[18] found 5 per cent. who had to be rejected on this score. Hence it is that the 13.1 per cent. rejected for heart disease by the local boards and induction examiners[19] did not include all even of the obvious and striking cases of cardiac disease, let alone those with nephritis and hypertension. In some states, where the examination was probably conducted more carefully, the figure rose as high as 22.8 per cent. Under the circumstances, then, remembering how highly diluted these percentages are by the number of cases in which the heart was not examined, we must be impressed by the high incidence of cardio-vascular disease in the young men of the nation.

In the discussion on Dr. Fisher's paper, Dr. Van Wagenen pointed out that 40 per cent. of 17,500 deaths studied by his company were traceable to cardiovascular-renal disease in one form or another, (1917, p. 259). As he said, "It makes little difference to us whether a man begins the circle of disease with an apoplexy, a chronic heart trouble or kidney disease; if he lives long enough he will develop all those different troubles." As we know that many of those who come to their end on account of hypertension, arteriosclerosis, heart and kidney disease are reported as having died of pneumonia, acute dilatation of the stomach, etc., we must suspect that at least one-half of all deaths are attributable to chronic cardiovascular disease. If, as I believe, the

16. Maclean: Brit. M. J. **1**:94, 1919.

17. Second Report of the Provost Marshall General, Washington, 1919, p. 424.

18. Whitney: J. A. M. A. **71**:1389 (Oct. 26) 1918.

19. War Department Bull. 11, 1919, p. 84. Physical Exam. of the First Million Draft Recruits.

tendency towards these troubles often exists from birth, then, if we look carefully enough, we need not be surprised if we find slight hypertension or other related peculiarities in about 50 per cent. of young men. I shall discuss shortly a possible explanation for the fact that these defects show up so much later in the women.

The main hope in attempting to define an upper limit of normal is that we may be able later to say from experience that if a boy has a pressure above a certain figure he is going, if he lives long enough, to develop definite cardio-vascular disease. It may prove impossible to prophesy about those with low pressures because some, perhaps, will develop hypertension in middle life, while others will live on past 70 with remarkably good arteries and kidneys. We will have to follow for the next forty years a large series of young men with apparently normal cardiovascular systems before we can say how many develop the degenerative diseases late out of a clear sky, and how many appear to develop them late, but really have shown a few signs and symptoms from childhood. The insurance directors who re-examine and follow up their cases will undoubtedly be able later to answer many of these questions. In the meantime we can learn a great deal by taking very careful histories on those past middle age who come now with hypertension. Not infrequently I get histories of "heart trouble," "kidney trouble," polyuria, dyspnea, palpitation, anginoid pain and "nervous breakdowns" dating back into childhood or years before the patients discovered their hypertension. Naturally in many instances this history can be gotten only from the mother. She will recall diagnoses and symptoms which caused her great anxiety during trying periods of her child's development. A review of the literature shows that chronic nephritis is not so uncommon in childhood and in many of the reported cases no infectious or other cause could be found.[20] We must analyze a large series of these histories to see whether the children of people with cardio-vascular disease are more likely to develop endocarditis and nephritic infections after the exanthemata than are the children of those with good hearts and kidneys. The bacteriologists are now awaking to the fact that the virulence of organisms is not the only variable and the resistance of the guinea-pig a constant. They are beginning to suspect that particularly when studying susceptibility to chronic infections, they must have to develop pedigreed strains of animals whose reactions to disease will be uniformly high or uniformly low. It is unfortunate that his training makes the city specialist look at his patient as a lone man making a short "to a finish" fight with bacteria. In many instances what the physician sees is but one round

20. Hill: Am. J. Dis. Child. **14**:267 (Sept.) 1917.
Berkeley and Lee: Am. J. Dis. Child. **13**:354 (April) 1917.
Judson and Nicholson: Am. J. Dis. Child. **8**:257 (Sept.) 1914.

of a fight which began years before and which will drag on until old age appears on the scene. Moreover, the patient is not alone but is surrounded by the shades of many ancestors who are making the fight hopeless either for him or for the bacteria.

SEXUAL DIFFERENCE

We come now to a discussion of the big sexual difference in blood pressure. As I stated above, the distribution curves suggest strongly that if there are two types in the community, we may say that the women before the menopause appear to be composed almost entirely of the type endowed with a low pressure. This uniformity is seen also in the fact that half of their readings fall within limits of 7 mm. on each side of the average. The interesting thing is that after 35, the women's distribution curve widens out so that it comes to resemble that for the men. We know that this big increase in blood pressure often comes at the menopause when the ovaries atrophy. It suggests that in some way the ovary is able to cover up or hold latent the tendency to hypertension which we will presume the women inherit equally with the men. Another possibility is that hypertension is a defect linked up, as are some other well known defects, with sex chromosome. This might explain why it appears early in the males who have only one such chromosome. The females have two, one of which may be normal and able to neutralize the defect in the other. With the atrophy of the ovary at the menopause the defect may appear, much as the plumage of a cock appears sometimes in hens with diseased ovaries. Much in favor of these theories is the observation that hypertension often develops early in women who show signs of insufficient ovarian function, such as scanty and painful menstruation, sexual anesthesia, male distribution of body hair, infantile uterus, etc. We shall have to check these observations statistically to see whether or not the correlation is close enough to be significant. Careful studies will have to be made also on families to ascertain the incidence of hypertension (1) when neither parent has cardiovascular disease; (2) when one has it, and (3) when both have it. I have already collected some records which show that the incidence of hypertension in children is likely to be very high when both parents show the defect.

We must also study in childhood the beginning of the sexual difference in blood pressure. Unfortunately, although considerable work has been done on blood pressure studies in children, I can find no data so arranged that we can say when the divergence appears. Some writers give their impression that it appears about the age of puberty, which is just what we should expect. If this point is settled definitely we shall be able to associate hypertension very closely with the evolution of sex and thus with the glands of internal secretion. It is inter-

esting to note in Figure 8 that the big increase in the incidence of hypertension comes 10 years later in the men than in the women. Apparently, the strenuous life has less to do with this disease than has the quieting down of the sexual functions.

<div align="center">PROGNOSIS</div>

What does slight hypertension mean in youth? Many will answer absolutely nothing. We know that these people can live out their three-score and ten and can work hard physically and mentally. I agree entirely with Sir James MacKenzie, Sutherland [21] and others who decry the tendency on the part of many physicians to treat these young people with "functional" cardio-vascular disease energetically with drugs, restricted diets and restriction of activities. Until we know more about the causation of the trouble, it does not seem to me that we have the right to prescribe minutely or to threaten the patient with disaster if he does not follow our instructions. Many of these boys enjoy athletics and we have as yet no data to show that such exercise will shorten life. We have no data showing that a protein poor diet persisted in for forty years will lengthen life. About all we can say is that as these people often tend to break down nervously, they should live within their means of strength; they should get enough sleep and rest, and should avoid nervous strain.

Although the experience of men like MacKenzie who have watched young people with murmurs, tachycardias, extrasystoles, transient albuminurias, etc., for long periods of time shows that the prognosis is generally good as regards the immediate future, I cannot accept their statements that these things mean nothing at all. In one instance a patient expressed it very well. He was a well built athletic young man of 24, a nervous wreck on account of a slight hypertension associated with extrasystoles and palpitation. He said, "All doctors who see me tell me to forget it, that there is nothing the matter with me; but I know that my uncles all had this sort of thing and they all died young with myocarditis. Now, if I live long enough won't I go the same way?" The fact that some obscure infection took him off three months later suggests that his presentiments of impending dissolution were not so unfounded and neurotic as most of his physicians thought they were.

Although people with hypertension can round out fairly long lives, the statistics of the life insurance companies show that in the aggregate this disease definitely shortens the expectancy of life. This is shown convincingly in Table 4 made up from data embodied in Fisher's paper (1915). This shortening of life is the more striking when we remember that these deaths took place within a period of at most eight years following the application for insurance. It is also signi-

ficant that it was cardiovascular disease which took off at least 78 per cent. of the men with the high pressures.

TABLE 4.—LIFE EXPECTATION IN PERSONS WITH HYPERTENSION *

	Per Cent.
Percentage of expected deaths according to American Actuarial tables......	100
Pressures of 105 and under...	47
Pressures of 106 – 110...	65
Usual experience in accepted cases..	86
10-14 mm. over average for age..	114
15-24 mm. over average for age..	181
25-34 mm. over average for age..	205
35-44 mm. over average for age..	246
45-59 mm. over average for age..	254
60 plus mm. over average for age..	450

* 2,857 cases were observed for periods of time ranging up to eight years.

Perhaps, we may look at it in this way: half of us are to depart from this world on account of cardiovascular disease. An ignorant, insensitive laborer may discover it at 60 when he has a stroke, or an acute decompensation of the heart. A business man, careful of his health, has his handicap discovered about the age of 40. A still more careful man may, perhaps, recognize in the circulatory disturbances of his little children the fore-runner of the process which, later in life, is to cause trouble. Many will ask, what good can come out of such pessimistic views? Several advantages may accrue. In the first place, we may learn a great deal about this disease by following it, not for a few months, but for a life-time or through several generations. Secondly, if we ever find specific methods for combating the process, it will probably be helpful to begin early; and thirdly, if we find that these diseases run through a lifetime we may spare our patients endless annoyance and financial loss in attempts at cures through tooth pulling, tonsil removing, purgation, sweating, use of drugs, high frequency currents, etc. Much light might be thrown on the etiology of the disease by studying the nature of the inheritance. Thus, if it be shown that not infrequently a man with a "pure hypertension" can have a father with marked arteriosclerosis, a mother with myocarditis, an uncle with nephritis and children with orthostatic albuminuria, and "functional murmurs," we will be in a position to say that these manifestations are probably all related.

It is to be desired that in the future those who write on this subject will give not only a few averages, but tables of frequency distribution so that their data can be used again and studied in other ways by subsequent observers.

SUMMARY

A statistical analysis has been made of the blood pressures in 8,737 University of California freshmen and 1,000 office patients.

The mathematical treatment of these data suggests that pressures over 130 mm. for the women and over 140 mm. for the men are abnormal. The arithmetical mean for women between 16 and 40 was 115 mm.; for men, 126.5 mm.

The blood pressure in young women is much more uniform than in men. The range for the women was practically from 85 to 155; for the men it was from 90 to 175. Fifty per cent. of the women's readings fell between 105 and 119 mm.; 50 per cent. of the men's fell between 116.5 and 136.5 mm.

High blood pressure appears earlier and to a greater degree in young men than in young women.

The average blood pressure in the women rose from 16 to 17; then dropped to 25 and after that rose rapidly. Little can be said about the men's yearly averages on account of disturbances in sampling brought out by the world war. Averages from the office patients showed that the pressure for women drops from puberty to 25, after which it rises so rapidly that the women catch up with and pass the men after 40. Apparently changes in the gonads of men and women have more effect on the blood pressures than has the strenuous life.

It is suggested that hypertension is based on a hereditary peculiarity. Its manifestations appear to be suppressed in women as long as the ovaries function well.

From clinical experience it would seem that pressures over 127 in women, and over 130 in young men, are indicative of a hypertensive diathesis which is associated with many typical symptoms and findings.

Fifty out of a hundred men will die of cardiovascular disease. This makes its appearance at different ages in the different men. The writer believes that careful examination would show the beginnings of such disease in childhood and youth, even in those individuals who are to round out a fairly long life. He believes that a hereditary predisposition is the most important etiologic factor.

Suggestions are made for further work along the lines of these hypotheses.

A METHOD FOR THE PERMANENT STAINING OF RETICULATED RED CELLS *

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BOSTON

In the clinical study of pathologic conditions of the blood and bone marrow, the recognition of immature forms of red cells is often of great importance. In specimens fixed and stained by the ordinary methods, the chief evidence of immaturity are the presence of nucleated, polychromatophilic and probably stippled red cells. With the possible exception of the nucleated erythrocyte, however, none of these forms has been generally studied with a view to obtaining a quantitative index of the variation in bone marrow activity. This is undoubtedly due to the fact that they are rarely found in normal blood, and that even in conditions in which a stimulation of the bone marrow may be assumed they may be present in very small numbers. In this connection considerable interest has been manifested in recent years in the so-called "reticulated cells," in which a fine or coarse network, or a fine granulation arranged in threads may be demonstrated by means of one of the vital stains. The normal number of these cells present in human blood is generally considered to be 0.8 per cent.

Among the first to observe this reticulation was Ehrlich [1] who, by means of a dried blood film stained with a saturated solution of methylene blue, described nets in the red blood corpuscle in cases of anemia and also under normal conditions. At this time he considered these nets an indication of degeneration of the erythrocyte. Askanazy,[2] twelve years later, using Pheln's stain, noted a reticulated substance in the erythrocytes of a rapidly progressing anemia but did not discuss their relation to the condition. In a still later paper [3] on the significance of megaloblasts in secondary anemia he mentions erythrocytes filled with a net-like structure but fails to mention the stain used in bringing them out. Apparently, the reticulation present in immature forms of red cells was generally unknown, or regarded as of little importance save for the two writers mentioned, as Ewing [4] in his

2. Ehrlich, P.: Berl. klin. Wchnschr. **3**:43, 1881.
2. Askanazy, S.: Ztschr. f. klin. Med. **23**:80, 1893.
3. Askanazy, S.: Ztschr. f. klin. Med. **27**:492, 1895.
4. Ewing, J.: Clinical Pathology of the Blood, Lea Brothers Co., Philadelphia, 1901.

book on the clinical pathology of the blood says: "Neither membrane nor reticulum have been fully demonstrated in the human red cell although both from analogy have been supposed to exist." In the same year Levaditi[5] started the use of brilliant cresyl blue as a vital stain, and although he describes the red cells there is no mention of reticulation. A year later Heinz[6] speaks of a regular network of chromatin and granules in the erythrocytes of embryos in fresh preparations stained with an Ehrlich-Biondi-Heidenhain mixture, but does not discuss the possible relation of the so-called network to reticulation.

From 1907 until 1913 the red cells gained considerable prominence, many clinics contributed work, either in regard to reticulation and polychromatophilia, or the source and significance of granules in erythrocytes. Cesaris-Demel[7] stained fresh blood with brilliant cresyl blue, and divided the extra nuclear material seen into substance A, reticulation; substance B, granules; and substance C, large round eccentric granules seen only in bloods which contain nucleated red cells. These substances were considered to be signs of youth of the cell which conception is held today. Meves[8] the same year described similar substances in the bloods of hens and guinea-pigs, stating that they are identical with the mitochondria of embryo sperm cells. Shipley,[9] working on the blood of embryo pigs, pictured practically the same material which he also called mitochondria; whereas Buchanan,[10] writing at an early period, was inclined to consider these different forms of the same substance. He said: "These so-called basophilic granulations may appear as dots, rods, irregular patches and as I have often noticed spiral markings. Erythrocytes of any shape either nucleated or nonnucleated may be thus effected."

Chauffard and Feissinger,[11] in experimental anemia, investigating hemolytic jaundice, describes the reticulated cells under the name "hematies granuleuses." Later Chauffard,[12] Widal[13] and his co-workers definitely established the relation of reticulation to familial hemolytic jaundice in which the reticulated cells may reach as high as 62 per cent. Biondi[14] is the first to state that reticulation and poly-

5. Levaditi, C.: J. de Physic et de Path. Gen. **3**:425, 1901.

6. Heinz, R.: Virchows Arch. f. Path. Anat. **168**:504, 1902.

7. Cesaris-Demel, A.: Folia hematol. **4s**:1, 1907.

8. Meves, F.: Anat. Anz. **21**:399, 1907.

9. Shipley, P. G.: Folia hematol. **21**:59, 1915.

10. Buchanan, R. J. M.: The Blood in Health and Disease, Oxford Medical Publications, 1909, p. 105.

11. Chauffard, M. A., and Feissinger, N.: Bull. et mem. Soc. méd. d' hôp. de Par., Nov. 8, 1907.

12. Chauffard, M. A.: Semaine méd., No. 5, 1908.

13. Widal, Ambri and Brule: Soc. méd. de hôp. de Par., Nov. 29, 1907.

14. Biondi, C.: Folia hematol. **5**:443, 1908.

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4
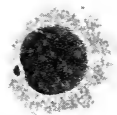
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Blood smear from a case of pernicious anemia. Nos. 1 and 2.—Nucleated red cells showing reticulation. Nos. 3, 4 and 5.—Various types of reticulated erythrocytes. No. 6.—A red cell which contains small particles of reticulation resembling stippling.
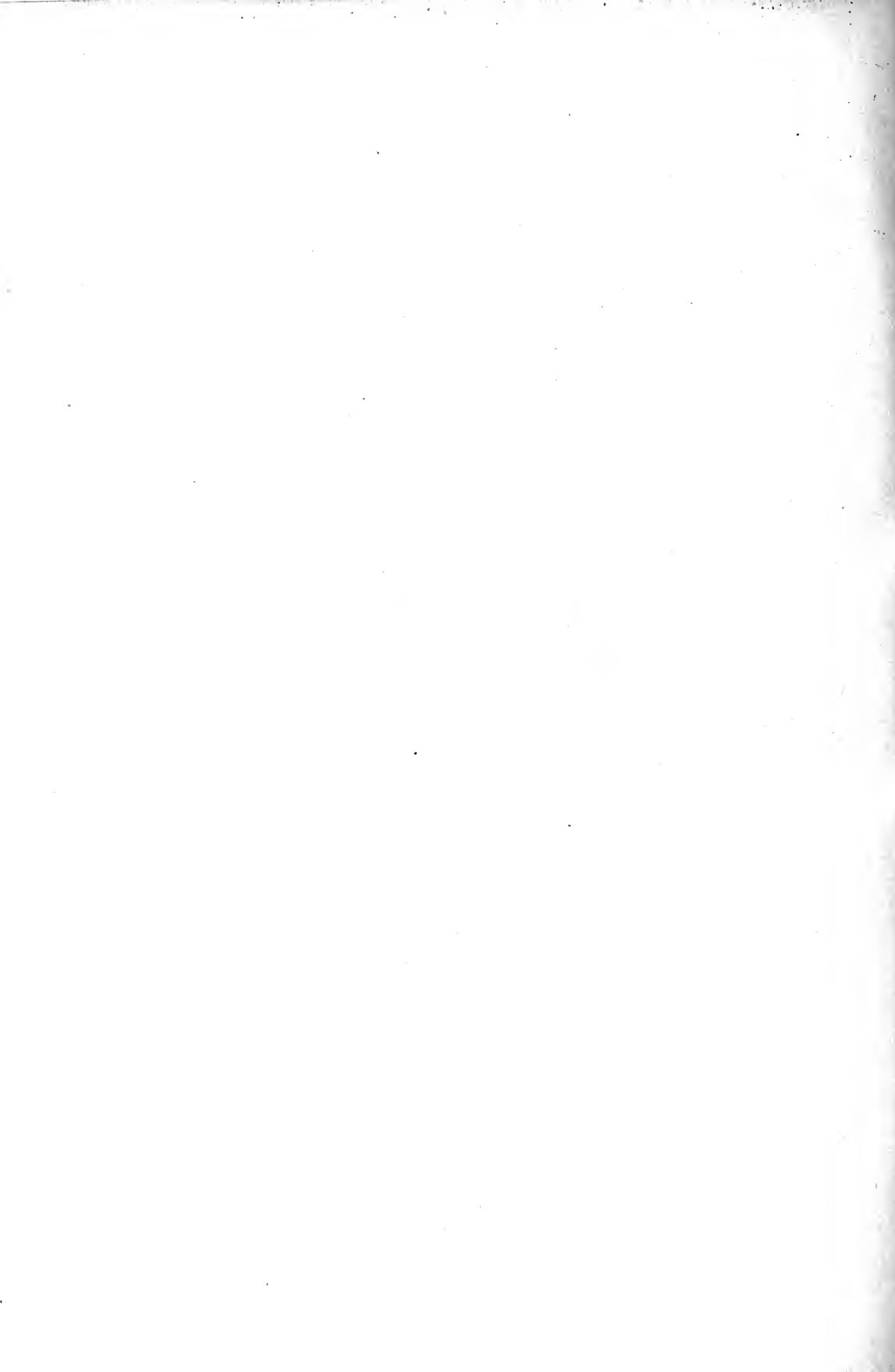
chromatophilia are the same, depending on the manner of staining. Pepper and Peet [15] agree with him. Cesaris-Demel [7] believed that the reticulation contributes to the formation of granules in the fixed preparation. Pappenheim [16] summarized the literature, agreed with Demel and concluded that reticulation is an evidence of youth of the erythrocyte, accompanies polychromatophilia but is surely not of nuclear or chromatic origin. In the same year Hawes,[17] working on the relation of reticulation, polychromatophilia and stippling, decided they were "but different forms of the same process." To part of this Schilling-Torgau [18] agrees, that reticulation and stippling are the same, but he does not retain the same view regarding polychromatophilia. Negreiros-Rinaldi [19] upheld Schilling-Torgau's opinion.

Clinically, the number of reticulated cells in a variety of conditions have been reported. Vogel and McCurdy [20] studied the blood of pernicious anemia patients before and after transfusion. Lee [21] and his co-workers also observed these cells in cases of the same disease, before and after splenectomy. Robertson,[22] working on the question of blood production, reported a diminution of reticulated cells during plethoric stages and an increase when there are signs of blood destruction. He, as well as Bock,[23] considered the percentage of reticulated cells of prognostic importance in cases of hemorrhage following wounds. Many cases of familial hemolytic jaundice are recorded with the usual high percentage of these cells. Harrop [24] recently showed that the oxygen consumption of blood which contains an abnormal number of reticulated erythrocytes has an oxygen consumption proportional to the percentage of reticulated cells present.

These observers did not enter into the question of the relation of reticulation to polychromatophilia and stippling, a relation which at present is rather obscure and undoubtedly requires further investigation in order to correlate the many widely divergent opinions. However, they share what seems to be the universal opinion, that reticulation is an evidence of blood regeneration and the percentage of these cells in the blood stream a reliable indication of the hematopoietic activity of the blood forming organs.

15. Pepper, O. H. P., and Peet, M. M.: Arch. Int. Med. **12**:81 (July) 1913.
16. Pappenheim, A.: Folia hematol. **7**:19, 1909.
17. Hawes, J. B. 2d: Boston M. & S. J. **161**:493, 1909.
18. Schilling-Torgau: Folia hematol. **1**:327, 1911.
19. Negreiros-Rinaldi: Arch. Ital. de biol. **66**:273, 1916.
20. Vogel, K. M., and McCurdy, U. F.: Arch. Int. Med. **12**:707 (Dec.) 1913.
21. Lee, R. I., Minot, G. R., and Vincent, B: J. A. M. A. **67**:719 (Sept.) 1916.
22. Robertson, O. H.: J. Exper. Med. **26**:221, 1917.
23. Robertson, O. H., and Bock, A. V.: Report of Shock Committee, Medical Research Committee, No. 25, March 14, 1919, p. 222.
24. Harrop, G. A., Jr.: Arch. Int. Med. **23**:745 (June) 1919.

The customary manner of observing reticulated erythrocytes is by the use of one of the vital stains, namely, brilliant cresyl blue, Janus Green B, Unna's polychrome methylene blue, crystal violet or methylene blue. The usual method of preparing a blood film is to mix a drop of the stain with an equal amount of blood, drop on a cover of glass, seal the edges with petrolatum and examine with the oil immersion lens. This type of preparation keeps only about three hours.

In this study, however, it was found that permanent preparations could be made by combining a vital with a Wright's stain. The reticulation is as clear, if not clearer, than by the older methods, and the Wright's stain retains all its differential qualities, except the polychromatophilia, which is not present. The ease and simplicity of this method brings the study of reticulated erythrocytes within the scope of routine blood examination.

The technic is divided into two stages. First, a small drop of a 0.3 or 0.5 per cent. aqueous or alcoholic solution of brilliant cresyl blue is placed on the end of a clean slide or the center of a cover glass, smeared around over an area 1.5 cm. in diameter with the aid of a match or glass rod and permitted to dry. After this is dry there may be a narrow margin of thick stain which should be wiped off with a damp cloth, leaving a central, uniform area. These slides or cover glasses may be prepared in large quantities, and if stacked side by side in a box and kept dry the stain will not deteriorate. The second stage consists of taking a drop of fresh blood on a clean coverslip and dropping it face down on one of the areas of dried stain. If the coverslip is clean the blood will quickly spread to the edges. The stain goes into solution almost instantly. (This preparation may be observed as a vital stain.) The cover glasses, or slide and cover glass, are now pulled apart as in making an ordinary blood smear and are permitted to dry. Smears may also be made by placing the drop of blood directly on the dried stain and spreading it with a cigarette paper or another slide. On drying, the blood turns a dirty greenish blue color. The slide or cover glass is then stained with Wright's blood stain. Too vigorous washing causes the reticulum to lose some of its stain. The preparation is dried in the usual manner and when mounted in Canada balsam keeps at least four months and propably much longer.

The reticulum is stained a deep or light blue, depending on its density, and gives a striking picture in its contrast with the pink protoplasm of the cell as shown in the accompanying illustration. Various types of reticulation are easily seen from the heavy skein-like material to knotted granular particles connected by delicate blue threads and finally the separate granules which resemble stippling

seen with Wright's stain alone. The nucleated erythrocytes in human blood usually have many fine threadlike blue staining filaments around, or radiating from the nucleus. There is no polychromatophilia seen. Whether the reticulation has replaced the polychromatophilia or not is a question requiring further investigation. The examination of many smears certainly suggests this as a possibility.

After this work was completed, it was found that Hawes [17] had used a similar method in 1909, that Schilling-Torgau [18] had used a similar but more complicated procedure, and that Pepper and Peet [15] stated that preparations could be made in this manner. However, the increasing interest in hematology, plus the importance and simplicity of this method, seems to warrant its presentation again.

ON THE BEHAVIOR OF THE PYLORIC SPHINCTER IN NORMAL MAN *

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Systematic studies of motor phenomena of the normal gastro-intestinal tract have been so largely carried out in the lower animals that but little detailed description of them in man is available. The results obtained from the studies in the lower animals can be applied only in a general way to the physiology of the digestive tract in man. It follows that more intimate knowledge concerning the motor phenomena of the alimentary canal in man would aid in the interpretation of results obtained from experimental studies of various phases of the pathologic physiology of human digestion. For this reason the work, with which the present report deals, was undertaken. It comprises observation on the behavior of the pyloric sphincter of the normal man in relation to various foodstuffs, and also to the presence of acid and alkaline solutions introduced into the stomach and duodenum of persons whose gastro-intestinal tracts were considered normal.

The results obtained from the latter observations bear particularly on the question of the "acid control" of the pyloric sphincter. The theory of the "acid control" of the sphincter was suggested by Pawlow,[1] among others, and was elaborated later by Cannon.[2] In epitome the theory is that the presence of acid in the antrum of the stomach causes relaxation of the pyloric sphincter, while the presence of acid in the duodenum causes the sphincter to contract. The evidences on which this theory are based were, again, obtained from experiments carried out on the lower animals. There are, however, phenomena occurring in the lower animals which it is admitted that the theory of acid control does not explain, and for this reason other controlling factors are assumed to exist. Whether or not acid or some other factor exerts the principal control of the pyloric sphincter in man has not been demonstrated by previous investigators.

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1. Pawlow: The Work of the Digestive Glands, London, 1902, p. 165.

2. Cannon, W. B.: The Acid Control of the Pylorus, Am. J. Physiol. **20:** 284, 1907.

METHOD OF OBSERVATION

1. The degree of contraction of the pyloric sphincter when food-stuffs partially fill the normal stomach was studied.

The data for this were obtained from fluoroscopic observations of normal human stomachs.

2. The behavior of the sphincter relative to the passage of carbohydrate, protein or fatty foods from the normal stomach into the duodenum was studied.

This was determined by fluoroscopic observations of the stomachs of normal persons after feeding meals composed of thick oat-meal porridge and barium, or 140 gm. of ground lean meat and 40 gm. of barium sulphate baked into a loaf, or 120 gm. of ground fatty bacon, 5 egg yolks and 40 gm. of barium baked into a loaf. The protein and fatty meals were of constant bulk and consistency.

3. Effect of the application of hydrochloric acid and sodium bicarbonate solution to the antral and duodenal ends of the pyloric sphincter on its functioning was studied.

Observations of the functioning of the sphincter were made by means of the fluoroscope.

The duodenal tube was given on an empty stomach and allowed to pass into the antrum in the region of the sphincter, or into the duodenum. Then a meal was fed. This was a meat and barium meal, either rinsed down with 200 c.c. of water or made into a thick mush by grinding in a mortar with water. In certain cases a malted milk, potato starch and barium mixture was also given. After the meal had been ingested fortieth normal, twentieth normal and tenth normal hydrochloric acid and 1 per cent. or 5 per cent. sodium bicarbonate solutions were introduced into the sphincteric region of the antrum or into the various portions of the duodenum, through the duodenal tube.

The subjects used were persons whose physical condition at the time of the observations was considered to be normal. The usual fractional clinical gastric analysis (Ewald test breakfast) showed no abnormalities.

1. The study of the degree of contraction of the normal pyloric sphincter, observed by means of the fluoroscope.

That the pyloric sphincter is closed when fluid food is in the stomach, except during the periods in which it opens to permit the ejection of food into the duodenum, was demonstrated in 1913 by Cole.[3] His observations were so readily and easily confirmed by fluoroscopic studies that they are now universally accepted. In this way the authors have confirmed Cole's observations a large number

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3. Cole, L. G.: Physiology of the Pylorus, Pilleus Ventriculi and Duodenum as Observed Roentgenographically, J. A. M. A. **61**:762 (Aug. 29) 1913.

of times. Further evidence that the normal quiescent sphincter is in a state of contraction is afforded by the following facts. By the use of considerable pressure on the abdominal wall, barium containing chyme can be forced from the stomach into the duodenum, as observed by means of the fluoroscope. This can be accomplished probably only when the sphincter has opened in relation to the advance of an antral peristaltic wave. When it can be accomplished the filled antrum and first portion of the duodenum are seen to be connected by a narrow isthmus of barium, which represents the sphincter; on cessation of pressure this narrow isthmus disappears.

When a fluid barium meal first enters the antrum of the stomach it frequently passes directly into the duodenum. Careful observation has shown that the barium does not fall through an open sphincter by means of gravity, but that from one to four small peristaltic waves are present in the antral region and that the pyloric sphincter opens in relation to the advance of a peristaltic wave; which latter seemingly ejects the barium into the duodenum.

2. The study of the behavior of the pyloric sphincter, observed by means of the fluoroscope, relative to the passage of carbohydrate, protein and fatty foods from the stomach into the duodenum.

By means of the fluoroscope a fluid carbohydrate meal, consisting of 500 c.c. of malted milk in which 90 gm. of barium sulphate are held in suspension by the aid of potato starch, is seen to start through the normal pyloric sphincter from at once to within a few minutes after it has been ingested. The normal sphincter opens regularly as each antral peristaltic wave approaches and permits the passage of barium containing chyme into the duodenum over a period of about ten seconds. In two normal young men the same phenomena occurred after the ingestion of thick oatmeal porridge mixed with barium. Except in pathologic conditions accompanied by pylorospasm, opening of the pyloric sphincter at irregular intervals, as described by Cannon in cats, was not observed. The regular opening and closing of the pyloric sphincter, except in the presence of pylorospasm, is so well known after the ingestion of fluid carbohydrate meals that no further observations on them were attempted in the present investigation.

Observations on the behavior of the pyloric sphincter after the ingestion of protein food were made in young men, ten normal, one with a quiescent duodenal ulcer, and one woman whose physical condition was normal. Similar observations were made after the ingestion of fatty food in eight normal young men. The duration of each experiment varied from one-half hour to six hours.

Since the results obtained in the various subjects were consistently uniform, only three of the experiments will be given in the following illustrative protocol.

REPORTS OF OBSERVATIONS

Protocol I.—*Observation 1.*—Male, aged 25.

MEAT MEAL

Meat and barium meal with 100 c.c. of water to drink.
5:25 p. m.: Began eating meal.
5:35 p. m.: Finished eating the meal.
Fluoroscopic observations; subject in reclining position.
5:35-5:38 p. m.: Gastric peristalsis active. As each wave approached the pyloric sphincter barium passed into the duodenum over a period of about 10 seconds.
5:45-5:47 p. m.: Ditto.
5:53-5:55 p. m.: Ditto.
6:00-6:05 p. m.: Ditto.

FATTY MEAL

Fatty and barium meal with 100 c.c. of water to drink.
6:07 p. m.: Began eating the meal.
6:14 p. m.: Finished eating the meal. The meal was nauseating to patient since he did not like fat; no nausea present after having eaten the meal.
Fluoroscopic observation; subject in erect posture.
6:14-6:16 p. m.: Gastric peristalsis active. As each wave approached the pyloric sphincter barium passed into the duodenum over a period of about 10 seconds.
6:21-6:24 p. m.: Ditto.
6:29 p. m.: Ditto.
Observation 2.—Male, aged 22.

FATTY MEAL

Bacon, egg and barium meal eaten as a dry loaf and without water to drink.
9:21 a. m.: Began eating the meal.
9:29 a. m.: Finished eating the meal.
Fluoroscopic observations; subject in erect position.
9:29-9:40 a. m.: Gastric peristalsis active. As each wave approached the pyloric sphincter barium passed through into the duodenum.
10:02-10:04 a. m.: Ditto.
10:28 a. m.: Ditto.
11:02 a. m.: Ditto.
Observation 3.—Male, aged 24. Meat and barium meal eaten as a dry meat loaf and without water to drink.
9:47 a. m.: Began eating the meal.
9:57 a. m.: Finished eating the meal.
Fluoroscopic observations; subject in erect position.
9:57 a. m.: Gastric peristalsis active. As each wave approached the pyloric sphincter barium passed through into the duodenum.
10:17-10:23 a. m.: Ditto.
11:09-11:12 a. m.: Ditto.
11:40-11:42 a. m.: Ditto.
12:35-12:37 a. m.: Ditto.

Observations on the various subjects, similar to the ones illustrated in the foregoing protocol, demonstrated that either the protein or the fatty meals began to leave the stomach within from three to ten minutes after the first mouthful of food was ingested; that is, as soon as the subject could ingest the meal and be prepared for fluoroscopic observation. The consistency of the food did not modify its initial leaving-

time. Furthermore, the food passed through the pyloric sphincter into the duodenum as each and every antral peristaltic wave approached that orifice, and during a period of about ten seconds. In the same subject no difference in the amounts, either of the same food or of the different foods, which passed through the sphincter at different times, was observed.

3. Effect of hydrochloric acid and sodium bicarbonate solutions on the opening and closure of the pyloric sphincter, as observed through the fluoroscope.

In observations on two subjects from 10 to 20 c.c. portions of twentieth-normal hydrochloric acid were repeatedly poured into the stomach almost on the antral end of the pyloric sphincter. No effect on the opening or closure of the latter could be observed. In a third subject a loop of the duodenal tube entered the duodenum in such a manner as to pull the metal tip up against the antral end of the sphincter. The pouring of 20 c.c. of this acid on the antral end of the sphincter resulted in almost complete cessation of gastric peristalsis on one occasion and, on another, complete pylorospasm developed without demonstrable disturbance in peristalsis. The introduction of 20 c.c. of 1 per cent. sodium bicarbonate solution was immediately followed by acceleration of gastric peristalsis; i. e., the duration of a wave decreased to thirteen seconds from twenty-two seconds. The action of the pyloric sphincter, as judged by its regularity of opening and the amount of barium which passed through it, was not affected. In an observation on another subject, 5 per cent. sodium bicarbonate solution was poured into the sphincteric region of the antral end of the stomach. The result obtained is outlined in Observation 3 of Protocol II.

The effect of the introduction of acid and alkaline solutions into the duodenum is outlined in Protocol II.

PROTOCOL II.—*Observation* 1.—Male, aged 26.

The patient complained of belching, occasional vomiting, pains in various regions of the abdomen associated with bowel movements, constipation, shooting pains in the chest, back and legs, and insomnia. Diagnostic studies were all negative After an Ewald test breakfast free hydrochloric acid was 15 and total acidity was 25. The patient was observed for two months and no evidence of organic disease was elicited during this period.

1 : 00 p. m.: Light lunch of toast, cereal and coffee. Duodenal tube swallowed.

4 : 00 p. m.: Subject was given 500 c.c. of barium, malted milk, potato starch mixture.

Fluoroscopic observations; subject in erect posture.

4 : 05 p. m.: Metal tip of duodenal tube in third portion of duodenum. It was pulled back into the first portion to a point just beyond the sphincter. Active peristalsis. Barium passed over in normal amount as each peristaltic wave approached the pyloric sphincter; 5 c.c. twentieth normal hydrochloric acid was quickly introduced through the tube as a gastric peristaltic wave

approached the sphincter and before the proper time for the sphincter to open. The sphincter opened and a normal amount of barium passed through into the duodenum.

Second observation twenty-four hours later.

Subject was not given food or drink for fourteen hours prior to introducing the duodenal tube.

8 : 25 a. m.: Duodenal tube swallowed; 85 c.c. of fasting gastric contents aspirated containing free hydrochloric acid 20.

11 : 25 a. m.: Meat and barium meal eaten. Metal tip of duodenal tube found in third portion of duodenum. Gastric peristalsis active. Barium passed over in normal amount as each peristaltic wave approached the sphincter. Five c.c. twentieth normal hydrochloric acid was introduced through the tube a short period before the proper time for the sphincter to open and when the duodenum was empty. Gastric peristalsis, the opening of the sphincter and the amount of barium which passed over were unaffected.

11 : 30 a. m.: Six c.c. twentieth normal hydrochloric acid were again introduced into duodenum a short period before the proper time for the sphincter to open and when the duodenum was empty. The same result occurred as in the preceding observation.

11 : 35 a. m.: The metal tip was pulled back into the first portion of the duodenum to a point just beyond the opening of the sphincter. Six c.c. twentieth normal hydrochloric acid were quickly introduced a short period prior to the time that the pyloric sphincter should open and when the duodenum was empty. The time of opening of the sphincter, the amount of barium passing through it, and gastric peristalsis were unaffected.

Observation 2.—Male, aged 28.

The subject complained of more or less constant mild headache. Diagnostic studies were negative. Fasting gastric contents: amount, 30 c.c.; free hydrochloric acid, 40; total acidity, 50. The patient had had a lumbar puncture several days prior to the observation. As a result he had a headache when in the erect posture, which disappeared completely on reclining. On the morning of the observation patient was given neither food nor drink.

9 : 00 a. m.: Duodenal tube swallowed.

10 : 10 a. m.: Began eating the meat and barium meal, which was ground up with water into a very thick mush.

10 : 17 a. m.: Finished eating the meat meal.

Fluoroscopic observations; subject in erect posture.

10 : 17 a. m.: Metal tip of duodenal tube in duodenum. Antral peristaltic waves very shallow.

10 : 25 a. m.: Antral peristalsis very weak, but a small amount of barium passed into the duodenum as each antral peristaltic wave approached the sphincter. Metal tip pulled back into third portion of duodenum.

10 : 40 a. m.: Subject nauseated, with moderately severe headache. Gastric peristaltic waves very shallow, and no barium passed through the sphincter. The metal tip was now found in the first portion of the duodenum just beyond the end of the sphincter.

The subject was now placed in reclining position on horizontal fluoroscopic table. His nausea and headache disappeared and about 15 minutes later antral peristalsis was active, and barium passed into the duodenum in easily demonstrable amount as each antral peristaltic wave approached the pyloric sphincter.

Fluoroscopic observations; subject in reclining position.

Metal tip in first portion of duodenum. Ten c.c. fortieth normal hydrochloric acid introduced beginning about five seconds before, and continued up to the time of opening of the sphincter. The sphincter opened normally, and also at the approach of the next two antral peristaltic waves.

Fifteen c.c. fortieth normal hydrochloric acid were now introduced under the same conditions as before. Sphincter opened normally and also at the

approach of the next four antral peristaltic waves. This procedure was now repeated twice with 20 c.c. of twentieth normal hydrochloric acid and with same result as noted before.

Twenty c.c. of 5 per cent. sodium carbonate solution were now introduced the latter part of the time the sphincter was open and up to the time of its complete closure. The sphincter closed normally and reopened normally. This procedure was repeated with 10 c.c. and then 15 c.c. of 5 per cent. sodium bicarbonate solution. The opening and closure of the sphincter were unaffected.

The duodenal tube was now washed with 60 c.c. of water (in 20 c.c. portions). For a few minutes following this, antral peristaltic waves became very shallow.

11 : 45 a. m.: Antral peristalsis active. Barium passing through sphincter in considerable amount with each antral peristaltic wave. During the periods barium was passing through the sphincter into the duodenum on three successive times the contents of the first portion of the duodenum were aspirated. Eight c.c. were obtained. This material was liquid, containing a small amount of barium and of meat fibers. Its acidity was: free hydrochloric acid, none (Töpfer's reagent); 5 c.c. neutralized 1 c.c. of tenth normal sodium hydrate. Hydrogen ion concentration = 5.60 (determined by potentiometer).

Observation 3.—Male, aged 47.

Subject had a mild type of chronic arthritis. At the time of the following observation the subject was in good health.

7 : 00 a. m.: A light breakfast was eaten.

1 : 00 p. m.: Duodenal tube swallowed, followed by a glass of water.

5 : 35-5 : 40 p. m.: Subject given one half of meat and barium meal and 450 c.c. of malted milk, potato starch and barium mixture.

5 : 48 p. m.: Antral peristalsis weak and but small quantities of barium pass into the duodenum as each peristaltic wave approaches the sphincter. Metal tip of duodenal tube in third portion of duodenum.

6 : 00 p. m.: Metal tip of duodenal tube pulled back into first portion of duodenum. This act resulted in almost complete cessation of gastric peristalsis for several minutes. After peristalsis again became active barium passed into the duodenum as each antral peristaltic wave approached the sphincter. On one occasion 5 c.c. and on three occasions 10 c.c. of fortieth normal hydrochloric acid and on one occasion 12 c.c. of twentieth normal hydrochloric acid (all warmed to 38 C.) were introduced into the first portion of the duodenum through the duodenal tube. Each portion of acid was introduced before and up to the time of opening of the sphincter in relation to the advance of an antral peristaltic wave. The introduction of the acid was not followed by a demonstrable effect on the opening of the pyloric sphincter, the amount of barium passing through it into the duodenum or on gastric peristalsis.

7 : 00 p. m.: Metal tip of duodenal tube pulled back into stomach and lay at the pyloric orifice of the sphincter. Forty c.c. of 5 per cent. sodium bicarbonate solution were introduced through the duodenal tube. The pyloric sphincter continued to open at the approach of antral peristaltic waves and barium was ejected into the duodenum in normal amount. Then the duodenal tube was washed by injecting 10 c.c. of water through it. Then 10 c.c. of gastric contents were aspirated and a few minutes later 2 c.c. more were withdrawn. Both these specimens were faintly alkaline to phenolphthalein.

Observation 4.—Male, aged 21.

Six years ago temporary jaundice had occurred following an attack of malaria. Beginning two years ago and lasting until one year ago there had been attacks characterized by nausea, vomiting and diarrhea. These attacks occurred at intervals of from two to three months and persisted for from one to seven days. There had been no hematemesis, and no bloody, tarry or clay-colored stools. Six months ago jaundice again recurred. During this time there had been constipation.

Physical examination was negative, except for slight icterus of the sclerae. The laboratory examinations were negative. The urine contained no bile pigments. After an Ewald test breakfast the gastric contents showed free hydrochloric acid 14 and total acidity 70.

At the time of the present observation jaundice of the sclerae had disappeared and the patient was free from symptoms.

On the morning of the observation the subject was given neither food nor drink.

8:00 a. m.: Duodenal tube swallowed, followed by a glass of water.

10:15-10:20 a. m.: Meat and barium meal eaten with 200 c.c. of water to drink.

Fluoroscopic observations; subject in erect posture.

10:30-10:40 a. m.: Metal tip of duodenal tube is in the third portion of the duodenum.

Gastric peristalsis regular and active. Pylorospasm was present and no barium passed through into the duodenum.

10:47-11:00 a. m.: Peristalsis active. A very slight amount of barium passed through the sphincter as each peristaltic wave approached that orifice. Subject placed on right side in the reclining position.

11:02-11:20 a. m.: Subject in the reclining position. Fluoroscopic findings during this period remain the same as in the preceding observation.

11:35 a. m.: Subject in the reclining position usual for fluoroscopic gastric examination. Metal tip of duodenal tube was at the junction of the second and third portions of the duodenum. Five c.c. of twentieth normal hydrochloric acid were slowly introduced beginning at the time of the starting of a peristaltic wave in the antrum and continued until a second similar wave had reached the pylorus. Both waves pushed barium through the sphincter in normal amount. The metal tip of the duodenal tube was now pulled back until it lay in the first portion of the duodenum, just beyond the end of the pyloric sphincter. Following this procedure gastric peristalsis ceased, except for some very shallow, feeble waves, which sent but a very small amount of barium through the sphincter into the duodenum.

After the lapse of a period of thirty minutes peristalsis again became active and barium in normal amount passed through the pyloric sphincter into the duodenum. Then 20 c.c. of twentieth normal hydrochloric acid were introduced slowly and continuously from the beginning of one antral wave until the end of the third. All three waves, as they approached the sphincter, were followed by the passage of a normal amount of barium into the duodenum. The same procedure was immediately repeated with a second 20 c.c. amount of twentieth normal hydrochloric acid and with the same result as noted before. A few minutes later peristaltic waves became weak and feeble and sent but a very small amount of barium through the sphincter.

After a period of about five minutes peristalsis again became active and barium passed through the sphincter in normal amount. The same procedure was repeated with 20 c.c. tenth normal hydrochloric acid and with the same results as before. After a few minutes peristaltic waves again became shallow and feeble and sent but small amounts of barium through the sphincter.

After about five minutes peristalsis again became active and barium passed through the sphincter in normal amount as each peristaltic wave approached that orifice. The same procedure was repeated with 20 c.c. of 1 per cent. sodium bicarbonate solution. No effect was noted on gastric peristalsis, the time or manner of the opening or closure of the sphincter or on the amount of barium which passed through it into the duodenum.

Observation 5.—Male, aged 35.

The subject had suffered with acute articular rheumatism, from which he had promptly recovered. At the time of the observation he was in normal health.

The subject was given neither food nor drink on the morning of the observation.

9:10 a. m.: Duodenal tube swallowed.

Fasting contents—amount 100 c.c., free hydrochloric acid, 50; total acidity, 60.

11:00 a. m.: Began eating one half of a meat and barium meal ground up with water into a thick mush.

11:07 a. m.: Finished eating half of the meal.

Fluoroscopic observations; subject in erect posture.

11:07 a. m.: Metal tip at first was in the third portion of the duodenum, and then slowly receded to the first portion. The movement of the metal tip was accompanied by pylorospasm which continued for ten minutes after its movement ceased. Antral peristalsis then became active and barium passed from the stomach into the duodenum as each peristaltic wave approached the pyloric sphincter.

Ten c.c. fortieth normal hydrochloric acid were introduced into the first portion of the duodenum before each opening of the sphincter in relation to the advance of two consecutive antral peristaltic waves (the acid was introduced before and up to the time of opening of the sphincter). No effect was observed on the opening or closure of the sphincter immediately following the introduction of the acid or its opening in relation to the advance of the three succeeding waves. Following the latter antral peristaltic waves became shallower and less barium passed through the sphincter. After peristalsis again normal 12 c.c. fortieth normal hydrochloric acid introduced under the same conditions. No effect on the opening of the sphincter in relation to the next four waves was observed. The patient now coughed and the next two waves were very shallow; but the next waves were again normal. Then 20 c.c. fortieth normal hydrochloric acid were introduced, and no effect on the opening of the sphincter in relation to the next six waves was observed.

12:10 p. m.: Duodenal tube washed with 5 c.c. of water and then emptied with air. Chyme flowing into the first portion of the duodenum on two consecutive openings of the sphincter was aspirated, about 8 c.c. were obtained. Subject was now given 300 c.c. of malted milk, starch and barium mixture. Then 20 c.c. of fortieth normal hydrochloric acid were introduced into the duodenum prior and up to the time of opening of the sphincter. No effect on the behavior of the sphincter was observed. Twelve c.c. of twentieth normal hydrochloric acid were now introduced as before, without effect on the opening of the sphincter. Ten c.c. 5 per cent. sodium bicarbonate solution were introduced into the first portion of the duodenum just before and during the opening of the sphincter and continued up until it closed completely. The sphincter closed normally. Twenty c.c. 5 per cent. sodium bicarbonate solution were introduced during the period the sphincter was open and up until it had closed. The sphincter closed normally.

In terms of normal acid the aspirated duodenal contents contained five hundredth normal free hydrochloric acid; the total amount of sodium hydrate neutralized was equivalent to an acidity of twenty-fifth normal, titrated to phenolphthalein.

DISCUSSION

In the observations outlined in the above protocol twenty-two observation were made on the effect of introducing acid solutions into the first, second or third portions of the duodenum. The time of the introduction of the acid in relation to the normal opening time of the pyloric sphincter varied. Acid was introduced: (1) a short period prior to the normal opening time of the pyloric sphincter in relation

to the advance of an antral peristaltic wave; or (2) at the time just mentioned and continued until after the sphincter had opened. for a second or third successive time.

In all the observations of the above protocol, the introduction of acid into the duodenum had no demonstrable effect on either the opening or the closure of the pyloric sphincter, on the amount of barium containing chyme ejected into the duodenum, or on gastric peristalsis. In Observations 4 and 5 the introduction of acid into the duodenum had no initial effect, but a late effect was noted. The latter consisted of partial cessation of gastric peristalsis. Moving the duodenal tube produced the same effect in these two observations and also in Observation 3, while in Observation 5 it produced pylorospasm on one occasion. These phenomena were interpreted as the result of abdominal irritation of the mucosa of the sphincter and duodenum due to movements of the tube. On this basis the partial cessation of gastric peristalsis, in Observations 4 and 5, may be explained; movements of the tube may have been produced by gastric and duodenal peristalsis. In this connection possible irritation of the duodenal mucosa incident to the introduction of fluid, its temperature, or its acid character must be considered. Irritation incident to the presence of the tube in the sphincter and duodenum can explain the pylorospasm present on the first observation in Observation 4. In two duodenal observations, on two subjects not outlined in the above protocol, the introduction of 20 c.c. amounts of twentieth normal hydrochloric acid into the first portion of the duodenum resulted in duodenal antiperistalsis associated with either prolonged pylorospasm or almost complete cessation of antral peristalsis. These phenomena were considered as the result of abnormal irritation of the duodenal mucosa resulting from the introduction of the acid. It will be remembered that mention has already been made of the development of pylorospasm and of partial cessation in gastric peristalsis after pouring twentieth normal hydrochloric acid onto the antral end of the pyloric sphincter.

The introduction of 5 per cent. sodium bicarbonate solution into the first portion of the duodenum in Observations 2 and 5, and 1 per cent. solution in Observation 4, produced no effect on the opening or closure of the pyloric sphincter, on the amount of barium passing into the duodenum, or on gastric peristalsis.

SUMMARY

Observations illustrated in Protocol I demonstrate that finely divided foodstuffs, either of carbohydrate, protein or fat, do not differ in the initial time at which they begin to leave the stomach and pass into the duodenum. This initial leaving time was not affected by variations in the consistency (viscosity) of the various foodstuffs. The food

was passing through the sphincter by the time the subjects could ingest the meals and be prepared for fluoroscopic observation; i. e., in from three to twelve minutes.

The barium containing chyme passed through the pyloric sphincter as each and every peristaltic wave approached that orifice. It continued to pour through the sphincter for a period of about ten seconds and then closed completely. The opening of the pylorus at irregular intervals, as described by Cannon [4] in cats, was not observed. The regular opening of the sphincter in man was observed by Cole,[5] but unfortunately his publication gives no experimental details.

In the five duodenal observations outlined in Protocol II the introduction of acid into the duodenum did not prevent the opening of the sphincter, or produce its closure. The amount of free acid present in the first portion of the duodenum is slight; in two subjects it was present in the concentration of eighty-fifth normal and five hundreths normal, and in another (Observation 2) no free hydrochloric acid was present. The acidity as titrated to phenolphthalein is low; expressed in terms of normal acidity, twenty-fifth normal, fiftieth normal and twentieth normal were found. These findings confirm those of McClendon and Myers.[6] The latter observers determined the hydrogen ion concentration of the duodenal contents. Their findings showed that a low degree of acidity was usually present. From this discussion it is obvious that the amount of acid introduced in these observations was always much in excess of the amounts of free hydrochloric acid present normally in the duodenum and its titration value varied from a lesser amount to an excess in relation to the total acidity, titratable to phenolphthalein, normally present. Furthermore, as shown in Observation 2 of Protocol II the titration value of the total acidity of the duodenal contents is no index to its hydrogen ion concentration. It may, therefore, be stated that the amount of acid introduced was always of a hydrogen ion concentration much in excess of that normally present in the duodenum. These observations do not support the theory that acid in the duodenum is the principal factor causing contraction of the pyloric sphincter.

In Observations 2 and 5 chyme was collected as it entered the first portion of the duodenum. The concentrations of hydrochloric acid in the chyme in the two observations were none and five hundredth normal, and total acidities titrable to phenolphthalein were equivalent to fiftieth normal and twenty-fifth normal. In these observations sodium

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4. Cannon, W. B.: Movements of the Stomach Studied by Means of the Roentgen Rays, Am. J. Physiol. **1**: 359, 1898.

5. Cole, L. G.: Am. J. Physiol. **43**:618, 1917.

6. Myers, F. J., and McClendon, J. F.: Note on the Hydrogen Ion Concentration of the Human Duodenum, J. Biol. Chem. **41**:187, 1920.

bicarbonate solution was poured into the duodenum after the pyloric sphincter had opened and up until the time of its complete closure. The amounts of sodium bicarbonate solution introduced were sufficient to neutralize, in the concentrations in which it was found to be present, a quantity of acid several times greater than the cubic contents of the first portion of the duodenum. For this reason, it is safe to assume that the contents of the duodenum were alkaline in reaction. Then, according to the "acid control" theory, the sphincter should have remained patent as long as the duodenal contents were alkaline. This it did not do, but was observed to close completely. Similar results were obtained in Observation 4. However, absolute evidence that the amount of carbonate solution introduced in the observation neutralized all the acid in the duodenum was not obtained, although but little doubt can reasonably exist but that neutralization was effected. In Observation 3, in which the gastric contents in the region of the sphincter were alkaline, the contents of the duodenum are known positively to have been alkaline. Nevertheless, there was no demonstrable effect on the opening or closure of the pyloric sphincter.

Since the sphincter opens in relation to the advance of each antral peristaltic wave the contents of the antrum are not undergoing a mixing process between the times of opening of the sphincter, as was described by Cannon [4] in cats. For this reason the degree of acidity of the antral contents must be constant during the interval in which the sphincter is closed. That the contents are acid is known. This statement is based on the following facts:

1. The authors, among others, have found the food when first ejected from the stomach into the duodenum to be slightly acid.

2. The contents aspirated from the stomach, after feeding various kinds of meats [7] and after the Riegal test meal [8] of meat and potatoes, are acid and contain free hydrochloric acid.

3. Free hydrochloric acid is constantly present in the stomach after feeding the Ewald test breakfast of bread and water.

From the above it follows that in order for the stimulation of acid in the stomach to open, and in the duodenum to close, the sphincter, there must be assumed the existence of a very delicate balance between the antral and duodenal reflexes in relation to the presence of acid, the duodenal reflex being much the more sensitive.

McClendon and Myers [6] and the authors have found the contents of the first portion of the human duodenum to be either neutral or of low acidity. After emptying itself of food just ejected from the

7. Fishback, H. R.; Smith, C. A.; Bergheim, O.; Lichtenthaeler, R. A.; Rehfuss, M. E., and Hawk, P. B.: Gastric Response to Foods, Am. J. Physiol. **49**:174, 204, 222 and 254, 1919.

8. Riegel, F.: Die Erkrankungen des Magens, Wien. **1**:123, 1903.

stomach the duodenum will, therefore, be practically neutral in reaction, and in the presence of pancreatic juice possibly alkaline. Then, if acid in the stomach causes the sphincter to relax, the sphincter should become patent when the duodenum empties itself of food. That the sphincter does not relax is demonstrated by the difficulty experienced in pushing barium through the sphincter into the duodenum by palpation of the abdominal wall. In fact, as has already been stated, it is probable that barium can be forced into the duodenum by this means only when the sphincter opens in relation to the advance of an antral peristaltic wave. From this it follows that, if the pyloric sphincter is under "acid control," then the fact that it opens at regular intervals and normally only in a definite relation to the advance of an antral peristaltic wave makes it necessary to assume: (1) either that there is a finely adjusted acid regulatory mechanism in the antral region of the sphincter which produces the proper degree of acidity to relax the sphincter at a fairly exact time in relation to the approach of a peristaltic wave toward the sphincter; or (2) that a comparable mechanism for properly neutralizing the contents of the duodenum must exist. If either or both such mechanisms exist they must be so adjusted as to permit of changes in the rhythm of the time of opening of the sphincter as occurred in one of our observations after pouring alkali onto the antral end of the pyloric sphincter. Furthermore, while the sphincter closes suddenly it remains open an appreciable length of time. Barium flows through the sphincter as an antral peristaltic wave approaches and continues to do so until the wave has spent itself. The sphincter, therefore, does not close as soon as acid enters the duodenum, and the presence of acid we have demonstrated. If acid in the duodenum causes closure of the sphincter then: (1) either the proper degree of acidity must be developed always at a time when an antral wave has spent itself; or (2) a secondary mechanism in some way regulating the reflex must be assumed.

The existence of the various factors outlined are necessary to explain the theory of "acid control" of the sphincter and their existence has not been proved. The assumption of the existence of these factors renders the mechanism of the control of the sphincter exceedingly complex. It is possible that some other less complicated mechanism may exist in man. The latter has been suggested, but not proved, by Luckhardt, Phillips and Carlson.[9] These investigators found a relation existed between the muscular activity of the antrum and the opening of the sphincter.

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9. Luckhardt, A. B.; Phillips, H. T., and Carlson, A. J.: Contributions to the Physiology of the Stomach; The Control of the Pylorus, Am. J. Physiol. **50**:57, 1919.

CONCLUSIONS

The conclusions which may be drawn from the observations here presented are as follows:

1. Finely divided carbohydrate, protein or fatty foodstuffs begin to leave the normal human stomach within a comparatively few minutes after their initial ingestion.

2. Under normal conditions the human pyloric sphincter opens regularly at the approach of each antral peristaltic wave, allows chyme to pass through into the duodenum during an appreciable length of time, and closes when the antral peristaltic wave has spent itself.

3. The introduction of fortieth normal, twentieth normal or tenth normal hydrochloric acid solutions into the first, second or third portions of the normal human duodenum either produced no effect on the opening of the pyloric sphincter as observed by means of the fluoroscope, or produced effects which were interpreted as the result of abnormal irritation of the duodenal mucosa.

4. Neutralization of the contents of the first portion of the duodenum did not prevent the closing of the pyloric sphincter.

5. The results obtained indicate that acid is not the principal factor controlling the opening and closure of the pyloric sphincter in man.

THE HEART IN SCARLET FEVER *

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During 1913 to 1919, 1,770 scarlet fever patients were treated at Durand Hospital, and cardiac complications were observed in 106. This does not include instances of increased rapidity nor occasional slight irregularity. A relatively rapid heart was common and slight irregularity, especially during the third and fourth weeks, was frequently noted, but was associated with no other appreciable alteration in the cardiac function.

Of the 106 patients recognized as exhibiting more definite cardiac complications, twelve had valvular defects antedating the scarlet fever. In the remaining ninety-four cases, a diagnosis of myocarditis was made in eighty-eight, of endocarditis in four and pericarditis in three. (One patient had both pericarditis and endocarditis.)

The cases of myocarditis have been classified as mild, moderately severe and severe. Mild cases were those with persistent feebleness, rapidity or irregularity of the pulse, but with little other disturbance. The moderately severe cases included those with a higher grade of myocardial disturbance, sometimes with definite signs of cardiac dilatation. The severe cases were those in which the cardiac disturbances were so severe as to render the prognosis very doubtful. They were characterized by signs of cardiac dilatation, cyanosis and marked irregularity, feebleness and variations in the pulse rate.

Fifty-three of the cases of myocarditis were classified as mild; four patients died of causes not related directly to the heart. Of the fatal cases, two patients had extensive bronchopneumonia, one patient had enteritis, and the other, a child, 2 years old, had a constant temperature around 105 F. with acute nephritis and active delirium.

Thirty cases of myocarditis were moderately severe. All of these patients recovered. Five of the cases of myocarditis were classified as severe. One of these patients, a woman, aged 25 years, died. From the beginning her temperature ranged from 103 to 104 F. The first four days of her illness there was a severe exudative process confined to her left tonsil in which there were no diphtheria bacilli. On the fourth day, her heart seemed dilated, although her pulse was regular and of good quality. On the fifth day, the patient looked and felt

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better. On this day, at 11:40 a. m., the patient expelled a large amount of fluid given as an enema. Suddenly, at 11:45 a. m., she became cyanotic and pulseless, gasped a few times and died.

Another severe case was that of a man, aged 21 years, with moderate bronchitis but otherwise running the ordinary course of scarlet fever. On the seventh day, about 1 p. m., he suddenly complained of pain in the cardiac region and great difficulty in breathing. He coughed several times and the pulse, which was irregular and faint, became unobtainable at the wrist. Cyanosis was very marked and the hands were clammy; the face and forehead were covered with perspiration. The right border of the heart was two finger-breadths beyond the right of the sternum, and the left border one finger-breadth to the left of the nipple line, whereas on admission and previous to the attack the borders had been normal. The lungs anteriorly were negative. Because of his critical condition and because any turning caused severe coughing the patient was not turned on his side or face for the examination of the back. Forty hours later, however, posterior examination revealed no rubs and no consolidation. At 5:30 p. m., the right border of the heart was at the sternal line, but the left border was one finger-breadth to the left of the nipple line. Heart tones were faint and no murmurs or friction sounds were heard. Following the accident for the next twenty-four hours the temperature rose to 104 F., and the pulse varied between 140 and 164, gradually returning to normal in four days. The patient was discharged in good condition thirty days after the onset of his scarlet fever. Because of the sudden cardiac pain and severe embarrassment the absence of blood in the sputum and negative lung findings, the pathology seemed to be in the heart and the possibility of an embolism in a twig of one of the coronaries was considered.

Myocarditis seems most common during the latter days of the acute stage of scarlet fever and in early convalescence, but may appear at any time during its course. Two examples of rather late myocarditis may be cited.

REPORT OF CASES

CASE 1.—A physician, aged 28 years, had a severe laryngitis, marked angina, bronchitis and acute nephritis early in his illness. On the twenty-first day of illness, after his temperature had been normal eight days, he was allowed to walk about his room. The pulse, which had been between 62 and 80, now fell to 52 and 60, was irregular and often bigeminal; the heart borders were normal. There was a soft systolic blow at the apex not transmitted to the axilla. No abnormal pulsations were noted in the jugulars. Blood pressure, 112/60. Under rest in bed and digitalis the patient improved so that in three days the normal rate, around 72, was present and the irregularity was gone. He was discharged in good condition thirty-four days after the onset of his illness.

CASE 2.—A man, aged 22 years, on the twenty-eighth day developed a sore and red throat with temperature about 100 F. This temperature persisted for

two days, and on the thirtieth day the ankles were painful and swollen and two days later the knees. On the thirty-third day the lips and nails were noticeably cyanotic and the pulse distinctly bigeminal with a rate of 60. The left border of the heart was one inch beyond the midclavicular line in the fourth interspace; the right border was substernal. No murmurs were heard and there were no subjective symptoms. The blood pressure was 85/30. With rest in bed and digitalis, gradual improvement took place, and the patient was discharged in good condition on the fifty-second day after the onset of his illness.

In the patients with myocarditis, the ages ranged as follows: six were 2 years of age or less (19.4 cases per hundred of the same age), twenty-two were between 2 and 5 years (4.9 cases per hundred of the same age), thirty-eight were from 6 to 10 years (5.9 cases per hundred of the same age). Of the patients above 10 years of age, numbering 627, twenty-two had myocarditis, or 3.5 per hundred. In only six was the patient entirely free from other complications. The associated complications were: cervical adenitis, fifty-seven cases, of which four were extreme; suppurative otitis media, unilateral, eight cases, bilateral, seven cases; nephritis, twenty-five cases, four of which were severe and in two uremic symptoms were well marked; arthritis, ten cases; diphtheria present with scarlet fever on admission, four cases; bronchopneumonia, five cases; laryngitis, two cases; mastoiditis, two cases, both patients operated on; herpes labialis, two cases; ulcerative stomatitis, two cases; other complications were: infected finger, rhinitis, cervical abcess, furunculosis, pyorrhea alveolaris, gonorrheal vaginitis, rickets, epistaxis, severe neuralgia, lobar pneumonia, streptococcal septicemia and conjunctivitis. In four cases of diphtheria with scarlet fever it is likely that the diphtheria may have had much influence in determining the myocardial disturbance.

Pericarditis.—Pericarditis was detected only three times, or in 0.17 per cent of the cases. One of the cases seems sufficiently interesting for brief review.

CASE 3.—A girl, aged 4½ years, after being in the hospital thirty-two days and desquamating in a typical manner, had vomiting, fever, and a recurrent scarlet rash. Twelve days after this recurrence there was pain in the left shoulder and elbow, but no swelling. Two days after this arthritis there was severe pain in the precordium and ensiform region, a systolic blow was heard at the apex and the left heart boundary was in the anterior axillary line; the pulse was 130; no friction rub was detected. The right heart border was at the right sternal line. Blood culture was negative. Twenty-three days after the recurrence a harsh scratchy to and fro rub was heard over the cardiac area and two days later, following an attack of severe pain in the cardiac region and vomiting, death occurred.

At the necropsy the entire pericardium, both parietal and visceral, was covered by a fibrinous shaggy exudate, and about one ounce of serous fluid was present. The heart seemed large and the right side was dilated and the cavities full of soft blood clots. The walls of the left ventricle were thicker than normal, the endocardium smooth.

CASE 4.—A boy, aged 16, admitted three days after the onset, presented the picture of a severe toxic scarlet with intense eruption, injected eyes and palms and severe angina. He had pain in the right knee and later multiple arthritis developed with tenderness over the epiphyses' and swelling of the limbs adjacent to the joints affected. Pericarditis appeared early, and later pneumonia. Repeated blood cultures gave large numbers of hemolyzing *Staphylococcus aureus.*

Death occurred seventeen days after the onset.

CASE 5 is described under endocarditis, which was also present.

Endocarditis.—Four patients had endocarditis.

CASE 6.—A girl, aged 12, after the second week of scarlet, ran a temperature betwen 99.2 and 102 F. and complained of sore throat. The tonsils were large and the pharynx red. There was no exudate, and culture yielded no diphtheria bacilli, but abundant hemolyzing streptococci were present. The day after the sore throat appeared, the cervical nodes were swollen and two days after this the patient felt faint, pallor was marked and the pulse was weak and irregular. This condition was present for several days. She preferred the sitting position and often complained of a feeling of oppression in the precordium and occasionally in the upper abdomen. Several times these attacks were severe, requiring the administration of morphin. The temperature during this period ranged between normal and 102 F., the pulse beat varied between 92 and 132. Examinations of the heart during this period showed the right boundary about one finger breadth to the right of the sternum, the left in the midclavicular line; no murmurs and no rubs were detected. Sixteen days after the onset of the sore throat the temperature was again normal and the patient rested well. A systolic murmur at the apex was now heard, with accentuated second pulmonic findings not present on admission. No increase in the normal heart borders was present.

Forty-six days after the onset the patient was discharged in only fair condition. She had the findings of a mitral regurgitation and appeared thin and anemic. This case is probably a carditis and has been counted among the cases of pericarditis. Seen two and five weeks after her discharge, this patient was apparently little improved and the heart findings were the same.

CASE 8.—A girl, aged 7½ years, was very septic from the onset. She had a constant high temperature and rapid pulse, double suppurative otitis media, extreme cervical adenitis and a recurrent rash. Death occurred thirty days from the beginning of her illness and at necropsy a fibrinous endocarditis of the mitral valve leaflets and aortitis were present.

CASES 9 AND 10.—A boy, aged 13, and a girl, aged 16, had mild endocarditis and made good recoveries.

Systolic murmurs were frequently present in this series of cases of scarlet fever, but they were considered functional or relative, disappearing with convalescence.

Old valvular lesions.—In this series there were twelve patients who had old valvular heart disease. All recovered but one, although two had high grade acute nephritis, one of them with extensive edema and marked uremic symptoms. The one who died was a boy, aged 5½ years, with club fingers and cardiac findings of mitral insufficiency. He had a very severe scarlet fever with irregular and rapid pulse constantly at 106 or above.

DISCUSSION

Poynton [1] suggested that the scarlet fever virus may have a direct effect in producing the tachycardia, and Broadbent [2] thought that the nervous mechanism of the heart may be disturbed through the inhibition of the vagus because signs of myocarditis are so frequently absent. Changes in the heart muscle, however, are frequent in scarlet fever. Pearse [3] observed fatty degeneration of the heart muscle in about five out of nine children examined, and he frequently noted myocardial fragmentation. Weill and Mouriquand [4] have recorded a fatal case on the 14th day in which there was severe myocarditis confirmed at the postmortem examination. Gouget and Dechaux [5] described cases of sudden death in scarlet fever without any lesion of the myocardium. Stegemann's [6] examination of 49 cases seems particularly worthy of note. He concluded that "in severe toxic cases of scarlet fever of short duration, the parenchymatous changes in the heart muscle are slight. In the infectious form of long duration, in addition to the parenchymatous degeneration there are fatty degenerations and necrosis. Interstitial round cell infiltration of the heart was lacking in the short severe toxic cases, but was always present in the long infectious cases. In the stroma of the heart ganglia, round cell infiltration can be demonstrated in the first days of the disease; its intensity is dependent on the severity and duration of the disease. Fatty degeneration and necrosis of the nerve cell were observed on the first day of the disease. The number and size of the Nissl bodies were markedly decreased in the severe toxic cases, in contrast with the infectious cases. These facts seem to show that in the severe toxic cases of scarlet fever of short duration, the cause of the heart weakness lies in pathologic changes in the heart ganglia." Most of our cases of myocarditis occurred after the acute stage of scarlet fever.

Pospischill and Weisz [7] have considered pericarditis as the characteristic heart lesion of scarlet fever. While it is entirely possible that even with careful study we may have overlooked occasional cases of pericarditis, our experience leads us to believe that in the type of scarlet fever met with here in the past six years, pericarditis is not very frequent. Poynton [1] has shown that pericarditis and endocarditis often occur in rheumatic children or in children with a family history

1. Garrod, Batten and Thursfield, "Diseases of Children," London, 1913, p. 461-462.
2. Practitioner **82**:13, 1909.
3. Med. & Surg. Rep. Boston City Hosp., 1899, p. 39.
4. Weill and Mauriquand: Presse méd. **19**:17, 1911.
5. Gouget and Dechaux: Quoted by Poynton: Garrod, Batten and Thursfield, "Diseases of Children," London, 1913, p. 462.
6. Jahrb. f. Kinderh. **30**:491, 1914.
7. Pospischill and Weisz: Ueber Scharlach, Berlin, 1911.

of rheumatism, and he says that chorea, repeated arthritis, pains and nodules occur over a period of years following scarlet fever. He has shown that the infecting organism has not been the same in all cases of pericarditis and endocarditis and he inclines to the view that these lesions are the result of secondary infection, the probable channel usually being the throat.

Endocarditis was not so frequent in our cases as in some other series. Klose,[8] in a series of 856 cases found endocarditis twelve times. However, it may be that our cases were of much milder type than those of some of the series quoted in the literature as, for example, the mortality in Klose's series was 12.1 per cent., while our mortality averaged slightly below 4 per cent. Klose says farther that at necropsy three cases were found which had not been recognized clinically, and he remarks that this is in accordance with Henoch, who states that the condition is often found anatomically when unrecognized clinically. Bohn[9] observed that "endocarditis develops commonly while fever and exanthem are coming out." Nobecourt[10] during the war found that it occurred in seven of 278 French soldiers. While Poynton[11] does not say how frequently endocarditis occurred, his twenty-five cases are selected from the records of fifty years of the Hospital for Sick Children in Great Ormond Street from which one would infer that they were not frequent. Pearse[3] mentions endocarditis once in his anatomic diagnosis in his series of twenty-three necropsies. McCollum[12] observed cardiac murmurs and irregularities of rhythm in from 18 to 50 per cent. in three series of 1,000 cases each.

SUMMARY

1. Of 1,770 cases of scarlet fever there were 106 patients with recognized cardiac complications. Ninety-four of these developed during the course of the disease, twelve were instances of old heart disease.

2. Eighty-eight of the 106 patients, or 5 per cent. of all the cases, had myocardial complications. Fifty-three of these were mild, thirty-one moderately severe, and five were very severe. Myocarditis may occur at any time in the course of the illness but is commonest in the latter days of the acute stage or in early convalescence. Other complications seem to increase the incidence of myocarditis. Myocarditis was observed more frequently in the early years of life.

8. Klose: Ueber den Scharlach der Kinder, Strassburg, 1903.
9. Gerhard's Handb. d. Kinderk. **11**:272, 1877.
10. Nobecourt: L'endocardite scarlatinal, Presse méd. **26**:429, 1918.
11. A Contribution to the Study of Rheumatism, with Notes on Twenty-five Scarlatinal Rheumatisms, Quart. J. Med. **3**:15, 1909.
12. McCollum: Modern Med. **2**:334, 1907.

3. Pericarditis was present in three cases, 17 per cent. Two of the patients died.

4. Endocarditis was present in four cases, 0.22 per cent. Systolic murmurs of the apex were frequently present but were usually regarded as functional or relative. The low percentage of endocarditis as compared with the percentage of several other series may be due to the milder type of scarlet fever in which the case mortality was less than 4 per cent.

5. Unless very severe, old heart disease does not necessarily indicate a serious prognosis in scarlet fever.

HEMOLYSINS FROM PARASITIC WORMS

PRELIMINARY PAPER *

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It is a well known fact that anemia is frequently present in cases of intestinal helminthiasis. Numerous cases of severe anemia, clinically indistinguishable from pernicious anemia, have been reported by clinicians and ascribed to the presence of various intestinal parasites, the removal of the parasites by anthelmintic medication resulting in an amelioration of the symptoms and eventually in complete recovery. That the broad tapeworm (*Diphyllobothrium latum*) and hookworms (*Necator americanus* and *Ancylostoma duodenale*) may cause an anemia has been recognized for a long time. That other intestinal parasites, notably the large intestinal roundworm (*Ascaris lumbricoides*) and the whipworm (*Trichuris trichiura*), may likewise be destructive to the erythrocytes of the host has not been generally recognized although certain parasitologists have from time to time called attention to this point.

While the loss of blood in cases of infestation with nematodes may be accounted for in part as a result of the direct abstraction of blood by the parasites, such explanation is wholly inapplicable to cestodes, since the latter have no mouth and are therefore incapable of extracting blood. Yet the severest cases of anemia due to parasitic worms have been encountered in infestations with tapeworms, namely, *Diphyllobothrium latum*. The view that the cause of Diphyllobothrium anemia is a toxic secretion of the worms has been advanced by a number of investigators on purely *a priori* grounds, but direct experimental evidence sustaining that view has been furnished by Schaumann and Tallqvist.[1] These investigators obtained from macerated Diphyllobothrium material a hemolysin active in vitro as well as in vivo, which they regarded as the etiological agent of broad tapeworm anemia. The investigations of these writers mark the beginning of the experimental study of hemolysins from parasitic worms and have served as a stimulus to similar investigations concerning other more or less common intestinal parasites.

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1. Schaumann, O., and Tallqvist, T. W.: Ueber die blutkörperchenauflösenden Eigenschaften des breiten Bandwurms, Deutsch. med. Wchnschr. **24**:312 (May 19) 1898.

For some time past I have been engaged in investigations on hemolysins from parasitic worms. A preliminary account of the work with Ascaris has been published elsewhere (Schwartz [2]). Since the publication of this paper a number of other parasites have been investigated and found to contain substances that are hemolytic to blood in vitro. The parasites that have been studied by me are species of Ascaris, of Ancylostoma, a hookworm belonging to the genus Bustomum, species of Trichuris, species of two genera of anoplocephaline cestodes, and several other forms. The results obtained may be summarized briefly as follows:

1. Hemolysins from parasitic worms are closely bound to the tissues of the parasites and may be liberated by thoroughly grinding the worm material and extracting it in physiological salt solution.

2. The hemolysins are soluble in alcohol. Ether soluble fractions are hemolytic to red blood cells, but the fraction from which the ether soluble substances have been removed contains the major portion of the hemolysin.

3. The hemolysins are inactive at low temperatures (8 C.), are inactive in the presence of normal serum, are destroyed by heating for thirty minutes at temperatures ranging between 62 and 65 C., excepting the hemolysin from Ascaris, which is resistant to higher temperatures.

4. The hemolysins are not specific to the blood of their hosts, but destroy erythrocytes of other species of animals also.

So far as the chemical nature of hemolysins from parasitic worms is concerned, Faust and Tallqvist [3] came to the conclusion that the active principle of Diphyllobothrium hemolysin is oleic acid. Faust [4] has given the "oleic acid theory" considerable prominence by producing a marked anemia in dogs as a result of feeding them oleic acid. Flury and Schmincke [5] likewise record the production of anemia in dogs as a result of prolonged feeding with oleic acid. These investigators record an increased resistance of erythrocytes from oleic-acid-fed dogs to oleic acid which they ascribe to a predominance of cholesterin esters in the red blood corpuscles. Less critical investigators have applied the

2. Schwartz, B.: A blood destroying substance in *Ascaris lumbricoides,* J. Agric. Research, Dept. Agric., Wash. **16**:253 (March 3) 1919.

3. Faust, E. S., and Tallqvist, T. W.: Ueber die Ursachen der Bothriocephalusanämie. Ein Beitrag zur Pathogenese der perniziösen Anämie auf physiologischchemischer Grundlage, Arch. f. exper. Path. u. Pharmakol. **57**:367 (Nov. 21) 1907.

4. Faust, E. S.: Ueber experimentelle Anämien, Berl. klin. Wchnschr. **45**:2121 (Nov. 23) 1908.

5. Flury, F., and Schmincke, A.: Ueber das Verhalten der Erythrocyten bei chronischer Oelsauervergiftung, Arch. f. exper. Path. u. Pharmakol. **64**:126, 1911.

oleic acid theory to hemolysins from parasitic worms other than the broad tapeworm in a number of cases solely on the ground that ether extracts of parasitic worms are hemolytic. Flury,[6] whose studies on Ascaris constitute the most complete investigation on the chemical composition and toxicologic effect of a parasitic worm, was apparently influenced to a great extent by the work of Faust and Tallqvist, since he ascribes to the unsaturated fatty acids of Ascaris, and particularly to oleic acid, the most important rôle in the blood destroying property of extracts of this parasite. Bondouy,[7] on the other hand, attaches comparatively little significance to oleic acid as a cause of anemia in cases of infestation with Strongylus, and finds that alcohol soluble fractions of Strongylus material that had been previously freed from ether soluble substances are hemolytic. He states that he isolated from the alcoholic extract of Strongylus an alkaloid with very marked hemolytic properties, which he regards as the most important hemolytic principle of the worm.

The results obtained by me show very definitely that fractions of worms freed from ether soluble substances are markedly hemolytic. This indicates quite clearly that agents other than oleic and other fatty acids must be involved. The results obtained appear to be in harmony with the results of other recent investigations concerning the possible rôle of oleic acid in anemia. Thus, Csonka[8] attaches no special significance to fatty acids as agents of blood destruction, since he found that unsaturated fatty acids constitute 48 per cent. of the fatty acid content of normal blood. "As such acids exist in normal blood as well as in pathological conditions without anemia it is necessary to look further for the primary causes of toxic hemolysis." Beumer,[9] on the basis of experiments in feeding oleic acid to dogs, challenges the theory of oleic acid anemia and denies not only the alleged rôle of oleic acid in anemia but also denies the view that cholesterin esters occur in the blood of dogs fed on oleic acid.

Certain investigators do not attach much significance to the presence of hemolysins in parasitic worms and are not inclined to ascribe any etiologic importance to these substances so far as the secondary anemia of helminthiasis is concerned. The reason that is usually advanced in support of this negative attitude is that the mere presence

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6. Flury, F.: Zur Chemie und Toxikologie der Ascariden, Arch. f. exper. Path. u. Pharmakol. **67**:275 (March 26) 1912.

7. Bondouy, T.: Etude chimique du *Sclerostomum equinum,* Arch. de parasitol. **14**:5 (July 30) 1910.

8. Csonka, F. A.: The fatty acids in human blood and pathological conditions, J. Biol. Chem. **33**:401 (March) 1918.

9. Beumer, H.: Zur pathogenetischen Bedeutung der Olsäure bei Anämien, Biochem. Ztschr. **95**:239 (July 5) 1919.

of hemolysins in an organism does not afford sufficient proof that the hemolysins in question are capable of causing anemia. In support of this contention it is pointed out that hemolysins may be isolated from normal tissues of animals that show no evidence of anemia. Thus, Weinberg,[10] who is an ardent defender of the view that the anemia that is present in cases of infestation with hookworms is due to a hemolysin secreted by the parasites and presumably absorbed by the host, is not inclined to accept the view that the hemolysin from the broad tapeworm is of etiologic significance, and, in fact, classes it with hemolysins that have been isolated from normal tissues, the so-called "tissue lysins."

I have investigated some of the properties of hemolysins from parasitic worms with the view of determining whether or not they resemble tissue lysins. The latter have been characterized by Noguchi [11] as thermostabile, nonspecific, active at 0 C., and markedly susceptible to normal serum in the presence of which they lose their potency. Chemically, Noguchi considers tissue lysins to be soluble soaps. The hemolysins studied by me differ from tissue lysins in that their activity is diminished by low temperatures and completely inhibited by a temperature of 8 C. Furthermore, with the exception of the hemolysin from Ascaris, which is resistant to higher temperatures, the hemolysins studied by me are destroyed by heating for thirty minutes at a temperature ranging from 62 to 65 C. On the other hand, so far as nonspecificity and susceptibility to normal serum are concerned, the two groups of hemolysins have not been differentiated.

Inasmuch as my investigations appear to indicate that hemolysins from parasitic worms are closely bound to cells of the parasites and may be liberated after thorough grinding of the worm material, it would seem that these substances partake of the nature of endotoxins. Whether hemolysins from parasitic worms are actually liberated from the bodies of the parasites during the life of the latter or whether they are liberated only when the worms sicken and degenerate, as appears to be the case with the broad tapeworm, cannot be answered with certainty on the basis of our present knowledge. That the hemolysins in question are of etiologic significance in certain parasitic diseases appears probable, however, in view of the clinical findings in such diseases, namely, reduction in number of erythrocytes, reduction in hemoglobin content of the blood, pale mucous membranes, etc. It is also

10. Weinberg, M.: Toxines vermineuses, Bull. de l'Inst. Pasteur **10**:969 (Nov. 30) ; 1017 (Dec. 15) ; 1065 (Dec. 30) 1912.

11. Noguchi, H.: Ueber gewisse chemische Komplementsubstanzen, Biochem. Ztschr. **6**:327 (Sept.-Nov.) 1907.

of interest to note that Weinberg,[12] in histologic examinations of organs of animals infested with hemolysin producing nematodes, has found evidence that blood destruction occurs in vivo.

The view that parasitic worms secrete toxic substances that are absorbed by the host not only affords a better explanation of the toxic symptoms of helminthiasis than the theory of "reflex action," but also affords an explanation of certain aspects of the pathology of helminthiasis, which are inexplicable on the basis of any other view that has thus far been advanced.

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12. Weinberg, M.: Passage dans l'organisme des substances toxiques sécrétées par les helminthes (sclerostome, oesophagostome, ankylostome), Compt. rend. Soc. de biol., Par. **64**:25 (Jan. 17) 1908.

A METHOD FOR THE QUANTITATIVE DETERMINA-
TION OF PROTEIN IN CEREBROSPINAL FLUID *

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Unquestionably one of the most important tests in the examina-
tion of the spinal fluid is that for protein. While normally present
in small amounts, excess is probably always pathologic. To be sure,
a diagnosis seldom rests on protein determination alone, but, taken
together with other tests, a knowledge of the total protein content of
the cerebrospinal fluid is of great value in differential diagnosis.

It has been the experience of one of us that the tests for protein
are often performed inaccurately, and wrongly or insufficiently inter-
preted. The chief reason for this is that the tests ordinarily used,
such as trichloracetic acid, phenol, nitric acid, butyric acid, etc., give
a precipitate in normal fluids, and that considerable experience is
required to recognize normal from abnormal quantities of precipitated
protein. More difficult, even for those well trained in such examina-
tions, is the recording of those tests for intelligent comparison of
fluids from different patients or of fluids from the same patient on
subsequent days. Comparison of the results of different observers
on the same fluid is notoriously unsatisfactory. Hence, in the litera-
ture the symbols +, ++, +++, and the terms "weak," "strong,"
and "very strong" constitute the usual estimate of such a test. It
is to reduce protein determinations to a figure having numerical
significance that the method now in use at the Massachusetts General
Hospital is advanced.

Three types of quantitative protein tests have been employed: (1)
Those dependent on precipitation of a known amount of fluid, and
read in a calibrated tube, on standing or after centrifugalizing; in
general, the Esbach method. This type of method is readily adapted
to meningitic fluids, but not to fluids containing small amounts of
protein. (2) Those made by precipitation of the proteins and the
subsequent determination of nitrogen in the precipitate by means of
the Kjeldahl method. (3) Those made by subtracting the nonprotein
nitrogen from the total nitrogen (determined by the Kjeldahl proce-
dure). The second and third methods are time consuming, require
a relatively large amount of fluid and are, therefore, unsuited for
clinical use. (4) Methods dependent on precipitation of protein by
means of some reagent either with or without the aid of heat, and

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the subsequent comparison of the precipitate with one or more standards of known protein content, or against a substitution standard corresponding to a known protein concentration. Methods based on this principle have been described by Mestrezat,[1] who uses standards prepared from albuminous urine, and by Ravaut,[2] whose standards are prepared from colloidal silver chlorid. The fourth type of procedure is excellently suited for work with spinal fluid as it is rapid, requires a minimum amount of material, and when properly used gives results of even greater degree of accuracy than is required for most clinical work.

Our search for a suitable method for protein determination in spinal fluids was commenced about two years ago. During this period we have experimented with various procedures involving the measurement of the colloidal protein suspension. The results of this work have led us to look with disfavor on the so-called substitute type of standard and to adopt the use of standardized protein solutions. We have also not been favorably impressed with the principle, so often used in so-called "quantitative" protein methods, of comparing the precipitate produced in a spinal fluid by means of some protein precipitant with a row of test tubes containing the precipitates formed in solutions of various known concentrations of protein. Procedures of this nature are commonly used in the comparison of colors, and in this case frequently give results within about 5 per cent. of the theory. With colloidal suspensions, however, the ability to differentiate between different concentrations is not so great as in the case of colored solutions, so that the suspensions given by spinal fluids having concentrations of protein varying by as much as 30 per cent. frequently present a practically identical appearance.

During the past decade the nephelometer has come into general use among biological chemists for the measurement of colloidal suspensions. We have not, however, employed this instrument in our work on spinal fluids on account of the relatively large volume of material required to fill the tubes, and because it can only be used to advantage in a dark or semi-dark room, a piece of equipment which is frequently not available in fairly well equipped clinical laboratories.

METHOD

The quantitative method finally selected, which in our hands has given excellent results, consists essentially in the measurement, by means of a suitable colorimeter, of the turbidity produced by adding

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1. Mestrezat, W.: Le Liquide Cephalo-Rachidien. Paris, 1912.
2. Ravaut, P. et Boyer, L.: Nouveau Procédé de Dosage Rapide de l'Albumine dans le Liquide Cephalo-Rachidien. Presse Méd., **28**: 42, 1920.

a solution of sulphosalicylic acid to the fluid. Sulphosalicylic acid, as a reagent for the quantitative determination of proteins, has been employed by Kober[3] for the nephelometric determination of protein in milk, in digestion mixtures, and in spinal fluids, and by Folin and Denis[4] for the turbidimetric determination of albumin in urine. No particular originality is therefore claimed for our procedure, our only contribution to this part of the subject being the experimental work necessary to determine the best conditions for the use of this reagent with spinal fluid, as in this work it was desirable not only to obtain a correct analytical technic but also to secure our result with the minimum amount of material.

The detailed description of the method is as follows: Into a test tube of about 4 c.c. capacity, 0.6 c.c. of spinal fluid is measured. To this is added 0.4 c.c. of distilled water and 1 c.c. of a 5 per cent. solution of sulphosalicylic acid. The contents of the tube is then mixed by inversion (but not by violent shaking) and after being allowed to stand for five minutes the suspension is read by means of a suitable colorimeter against a standard protein suspension prepared at the same time as the unknown. This standard is made by adding to a test tube 3 c.c. of a solution containing 0.3 mg. of protein per c.c. and 3 c.c. of 5 per cent. sulphosalicylic acid solution. Our standard protein solutions have been prepared from fresh normal human blood serum by the following method: Twenty c.c. of serum is mixed with about 200 c.c. of 15 per cent. sodium chlorid solution, and the resultant mixture is filtered. The nitrogen of the mixture is then determined by the Kjeldahl method, and from this strong standard, which if preserved with chloroform in a tightly stoppered bottle, will keep for three months in the refrigerator, there is prepared by suitable dilution with distilled water, two dilute standards containing respectively 0.2 and 0.3 mg. of protein per cubic centimeter. These dilute standards, even when preserved with chloroform and kept in a refrigerator, are usually not reliable for a longer period than two weeks. We have found the 0.3 mg. standard to be suitable for a large majority of the fluids examined; occasionally, however, this standard is too concentrated when a fluid unusually poor in protein is encountered, and for such the standard containing 0.2 mg. protein per cubic centimeter may be employed.

In the directions given above we have stated that 0.6 c.c. of fluid should be used for this determination. While this is the amount found most convenient for use with the great majority of normal or approxi-

3. Kober, P. A.: J. Biol. Chem. **13**:485, 1913; J. A. M. Chem. Soc., **25**:290, 1913.

4. Folin, O., and Denis, W.: J. Biol. Chem., **18**:273, 1914.

mately normal fluids, it will frequently be found too great in fluids with an increased protein content. With such material it is frequently necessary to use 0.3, 0.2 or even 0.1 c.c. of fluid, and to add 0.7, 0.8, or 0.9 c.c. of water (in order to bring the volume of the diluted fluid to 1.0 c.c.). In fact, in fluids of extremely high protein content, such as may be encountered in cases of spinal cord compression, meningitis, etc., it is sometimes necessary to make a preliminary dilution with water as even 0.1 c.c. of such fluids may contain too much protein to read against the standard.
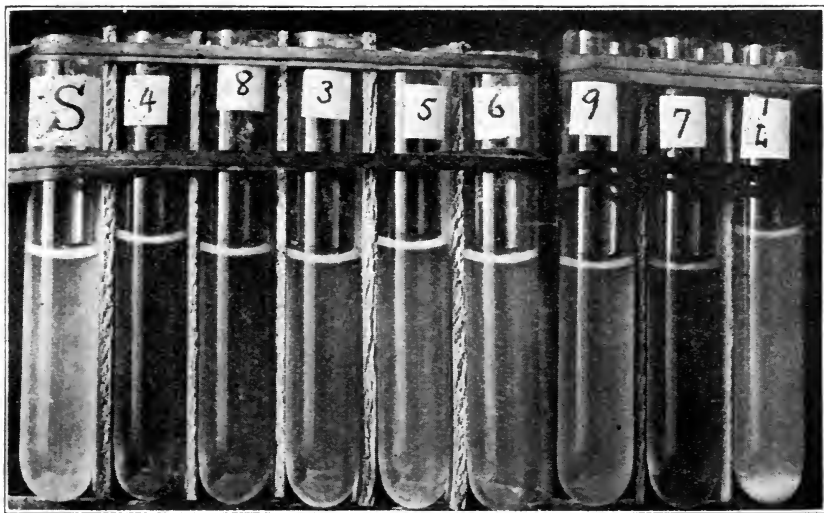
Spinal fluid precipitated according to this method and ready to examine. The photograph was taken approximately one hour after precipitation and shows all but one (1 L) in suitable colloidal suspension. (Note: The appearance of a precipitate is an optical error, due to reproduction, except in the tube marked 1 L).

S = standard; 4, 8 and 7 = normal amounts of protein. 3, 5, 6. 9 = active tabes; 1 L = acute meningitis. (This suspension is unsatisfactory for examination. Another more dilute should be prepared).

The colorimeter best suited to this work is the small model Duboscq with 30 mm. scale. As the cups of this instrument have a capacity of only 2 c.c., it is excellently suited for work in which only a small amount of fluid is available. It is also possible to use the Duboscq model with 60 mm. scale by providing an extra pair of cups with heavy glass walls, a device which greatly reduces the quantity of liquid needed to obtain a reading with this instrument. Whatever the type of colorimeter chosen, it is absolutely essential that before any attempt is made to read an unknown, the standard solution should

be placed in both cups and several readings made. When the operator has satisfied himself that he can read the standard against itself he should then - make readings of the unknown, taking care, however, that the position of the mirror of the colorimeter is not changed. It has been our experience that the most accurate results are secured when the mirror is adjusted to give the maximum illumination. Our readings have been made by means of a 100 watt tungsten lamp provided with a screen of ground glass.

Good results can be obtained when standard and unknown are of widely varying concentration, in fact when working with standard solutions we have found it possible to obtain good results with suspensions having variations as great as 75 per cent.; in practice, however, it seems safer to discard results in which the difference between the standard and the unknown is more than 30 per cent. The calculation of the results is simple. If the 0.3 mg. standard is used, multiply by 0.3 the quotient obtained by dividing the reading of the standard by the reading of the unknown, divide the product by the amount of fluid taken and multiply this quotient by 100. This calculation gives the result expressed in milligrams of protein per hundred c.c. of fluid.

The results obtained by the above procedure have been checked by the following method: Large composite samples of spinal fluid were obtained by mixing the results of lumbar puncture on a number of patients. In these composite samples we determined total nitrogen by the Kjeldahl method, total nonprotein nitrogen by the method of Folin and Wu[5] and total protein by the procedure described in this paper. The figure obtained by subtracting nonprotein nitrogen from total nitrogen gives a value which is considered to represent the nitrogen combined as protein. As will be seen from an examination of Table 1 the figures obtained by this method closely approximate those obtained by means of our turbidimetric readings.

TABLE 1.—RESULTS OF EXAMINATION BY KJELDAHL AND AUTHORS' METHODS

| | Mmg. Protein per 100 c.c. Fluid | |
Fluid No.	Total Protein by Our Method	Total Protein by Our Method
1	119.0	117.6
2	112.	111.
4	234.	235.

Three factors influencing the accuracy of the test or rendering it worthless must be mentioned: (1) A fluid contaminated with blood enough to be visible to the eye will in normal fluids give such high

5. Folin, O. and Wu, H.: J. Biol. Chem., **38**: 81, 1919.

protein readings as to be definitely abnormal. (2) Fluids with bacterial contamination will give unreliable results. (3) Fluids standing for long periods uncorked or with cotton plugs, even though clear, will give increasing amounts of protein from day to day. If kept corked and sterile, accurate determinations were obtained at intervals over a number of weeks.

CLINICAL OBSERVATIONS

The method of quantitative protein determination as outlined above has now been in use for six months, during which time we have had occasion to employ it in the examination of several hundred fluids. Owing to the uncertainty of exact diagnosis in many of the patients from whom fluids were taken, it seems unwise to be dogmatic regarding the protein level in different pathologic states, and Table 2 gives a general summary of the values obtained in cases in which we are most certain of the diagnosis, figures which we believe will be substantiated by further work.

TABLE 2.—PROTEIN LEVEL IN NORMAL AND PATHOLOGIC CEREBROSPINAL FLUIDS

Normal	35- 100 mg. per 100 c.c.
Ventricular Fluids (brain tumor cases)	under 100 mg. per 100 c.c.
Syphilis of the nervous system, inactive	50- 125 mg. per 100 c.c.
Active tabes and moderately active syphilis of the nervous system	100- 200 mg. per 100 c.c.
Acute syphilis of the nervous system and general paresis	200- 600 mg. per 100 c.c.
Lethargic encephalitis	100- 200 mg. per 100 c.c.
Recent cerebral vascular disturbances (hemiplegias, cerebral embolus, etc.)	100- 300 mg. per 100 c.c.
Tubercular meningitis	200-1000 mg. per 100 c.c.
Acute meningitis	400-1300 mg. per 100 c.c.
Fluid below spinal cord compression:	
"Nonne syndrome"	300-1700 mg. per 100 c.c.
"Froin syndrome" (one case)	2010 mg. per 100 c c.

Several cases of cord compression (tumors, etc.) have been investigated by combined lumbar and cisterna magna punctures in order to investigate the fluid above and below the level of compression. One such case, where compression was due to a cholesteatomatous cyst, is given as illustration of the marked difference in protein content. The cistern fluid gave 83 mg. per hundred c.c., the lumbar fluid 1,112 mg.

SUMMARY

A method is given for determination of total protein in the spinal fluid, accurate to within approximately 5 per cent. The method is

adapted to use in any well equipped clinical laboratory, and the technic can be readily acquired. It has the advantage that only a small amount of fluid is employed, that it is equally accurate with protein-poor or protein-rich solutions, and that a determination may be made in about ten minutes.

The advantage to the clinician is obvious; substitution or control of qualitative methods by a rapid and relatively accurate quantitative procedure.

BLOOD CHEMISTRY STUDIES IN INFLUENZAL PNEUMONIA *

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Heretofore studies in blood chemistry have chiefly been confined to cases presenting evidences of renal involvement. Cases of pneumonia and other infectious diseases have received little attention in this direction. This is due to the assumption that such studies would be of little value, and partly also to the relative newness of the subject of blood chemistry.

This report sets forth the findings in 131 specimens of blood from sixty-one cases of influenzal pneumonia, representing various degrees of severity, and obtained on various days of the disease. The results were obtained from forty-two nonfatal cases and sixteen fatal cases, thirteen patients receiving intravenous injections of hypertonic glucose solution and six cases receiving intravenous injections of foreign protein.

Nonfatal Cases: Table 1 includes the blood chemistry findings in forty-two nonfatal cases, arranged according to the day of the disease on which the blood was examined. In a few of these cases incomplete urinary findings are included. In seventeen cases the average excretion of chlorids per twenty-four hours was 2.98 gm.; in only one case was the finding in this regard normal. The above finding is in accord with the reported diminution of the urinary chlorids in pneumonia of the lobar type, and gives evidence that the same condition holds for influenzal pneumonia. In eleven cases the urinary urea averaged 21.46 gm. per twenty-four hours, which is within normal limits. In only one case was the amount subnormal, the blood urea in this case being slightly increased. In other cases in which the blood urea was considerably higher the content in the urine was normal. Unfortunately in the three cases in which the blood urea was highest the urine content was not determined. The severity of the pneumonia apparently had little influence on the amount of urea in the urine.

With the diminution of the chlorids in the urine one might expect to find an increase in the blood. Our findings in this regard coincide with those of Gettler,[1] in that we consistently failed to find an increase. In five cases, classed as mild and moderately severe, the blood chlorids averaged 0.70; the average for the forty-two nonfatal cases being 0.57 per cent.

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1. J. A. M. A. **71**: 2033 (Dec. 21), 1918.

The results of blood sugar determinations are included in the tables, but in the light of our present knowledge have little significance. It is to be noted, however, that a number of the cases gave findings toward the upper limits of normal. This may be caused by the injected glucose solution.

TABLE 1.—Blood Chemistry Determinations in Nonfatal Cases of Influenzal Pneumonia

Case Number	Urine					Blood Chemistry Findings								Remarks
	Albumin	Casts	Day of Disease	Chlorids, Gm.	Urea, Gm.	Day of Disease	Chlorids, per Cent.	Sugar, per Cent.	Creatinin, per 100 Blood, Mg. C.c.	Urea Nitrogen, Mg. per 100 C.c. Blood	Urea, Mg. per 100 C.c. Blood	Uric Acid, Mg. per 100 Blood	CO₂ Combining Power of the Blood Plasma	
1*	N	N	1	...	....	1	0.48	0.14	1.4	13.0	27.82	5.0	..	Very severe
2	N	N	..	...	....	1	0.49	0.12	1.75	15.75	31.705	2.95	..	Moderately severe
3	P	P	..	...	....	1	0.46	0.12	2.5	53.0	113.42	7.7	..	Very severe
4	P	N	..	...	....	1	0.60	0.17	2.1	17.2	36.8	6.1	..	Very severe
5*	N	N	3	1.7	....	2	0.74	0.12	0.85	18.0	38.52	2.2	..	Moderately severe
6	P	P	3	1.6	22.4	2	0.68	0.13	1.0	16.7	33.75	2.45	65	Very severe.
7	N	N	2	1.2	....	2	0.61	0.14	3.05	19.5	41.73	4.05	55	Moderately severe
8	N	N	4	6.8	20.6	2	0.64	0.13	0.85	20.7	44.29	2.2	52	Moderately severe
9	P	P	..	...	....	2	0.56	0.14	1.35	16.3	34.88	5.8	..	Moderately severe
10	N	N	..	...	....	2	0.60	0.16	2.10	47.1	100.79	18.1	..	Moderately severe
11*	N	N	27	...	17.0	2	0.57	0.14	1.2	12.2	26.1	5.2	..	Mild case
12	P	N	2	8.7	33.2	2	1.27	0.13	1.0	18.0	38.52	0.96	..	Moderately severe
13	P	N	3	4.2	9.29	2	0.63	0.16	1.35	18.0	38.52	2.9	56	Moderately severe
14	N	N	2	3.6	16.56	2	....	0.14	2.0	32.2	65.48	3.42	54	Moderately severe
15	P	P	..	...	....	2	0.44	0.10	2.6	16.25	34.77	1.72	..	Moderately severe
16	N	N	..	...	....	2	0.51	0.09	1.1	16.3	34.88	1.2	..	Moderately severe
17	P	P	..	...	....	2	0.46	0.12	2.5	53.0	113.42	7.7	..	Very severe
18	P	P	19	2.47	40.85	2	....	0.11	1.6	22.27	47.65	6.6	..	Very severe
19	N	N	3	1.4	11.6	3	0.61	0.17	1.7	25.2	53.92	14.3	..	Moderately severe
20	P	P	..	...	....	3	0.56	0.15	1.58	19.3	41.30	12.1	..	Mild case
21	P	N	3	2.1	....	3	0.49	0.15	1.9	16.2	34.66	2.5	..	Moderately severe
22	N	N	4	2.9	....	3	0.70	0.10	0.85	15.1	32.31	1.77	54	Mild case
23	N	N	..	...	....	3	0.44	0.13	1.5	19.5	41.73	2.6	..	Moderately severe
24	P	P	..	...	....	3	0.46	0.11	2.55	26.5	56.71	5.7	..	Very severe
25	N	N	..	...	....	3	0.49	0.11	1.55	19.5	41.73	3.2	..	Moderately severe
26	P	P	12	3.1	29.07	3	0.44	0.13	1.0	20.75	44.4	6.4	..	Very severe
27	..	..	..	...	....	4	0.68	0.11	1.5	28.0	59.92	2.7	..	Moderately severe
28	P	P	7	1.2	....	4	0.70	0.14	1.1	32.2	68.9	6.0	..	Moderately severe
29	N	N	..	...	....	4	0.48	0.10	1.1	13.0	27.82	3.2	..	Very severe
30	N	N	6	4.3	....	4	0.46	0.06	1.2	16.75	35.84	0.71	..	Moderately severe
31	P	P	6	0.6	....	5	0.64	0.13	1.05	32.0	68.48	4.2	45	Mild case
32	N	N	..	...	....	5	0.65	0.14	1.1	22.2	47.5	4.4	..	Mild case
33	N	N	6	3.2	20.8	5	0.53	0.13	1.1	17.5	37.45	...	..	Mild case
34	N	N	..	...	....	5	0.46	0.07	1.2	15.75	33.70	1.22	..	Moderately severe
35	N	N	..	...	....	5	0.45	0.09	0.55	16.75	35.84	0.66	..	Moderately severe
36	N	N	..	...	....	5	0.48	0.16	1.35	15.75	33.70	5.1	..	Moderately severe
37*	P	N	4	1.8	....	6	0.68	0.16	1.0	31.2	66.76	1.71	47	Moderately severe
38	P	N	4	...	14.7	6	0.74	0.11	0.75	15.2	32.52	2.65	62	Mild case
39	N	N	..	...	....	8	0.66	0.11	1.4	40.0	85.60	2.9	..	Moderately severe
40	P	P	..	...	....	10	0.58	0.12	2.2	13.0	27.82	2.9	..	Moderately severe
41*	N	N	..	...	....	11	0.70	0.09	3.5	19.0	40.66	1.7	..	Moderately severe
42	N	N	..	...	....	26	0.55	0.14	0.85	15.3	32.74	...	..	Very severe

* Cases in which pleurisy or empyema occurred.

Abnormal amounts of creatinin in the blood usually indicate renal involvement. Meyers and Lough [2] state that creatinin of 2.5 mg. or more per hundred c.c. of blood almost without exception indicates involvement of the kidneys. Five of the cases in this group had find-

2. Arch. Int. Med., **16**: 536, (Nov.), 1915.

ings above this amount, the highest being 3.5 mg.; two of these cases had neither albumin nor casts in the urine. The severity of the pneumonia apparently influenced little the retention of creatinin. In six mild cases the average was 1.09 mg. per hundred c.c. of blood, and in eleven very severe cases 1.57 mg., both figures being within normal limits.

Retention of urea nitrogen and urea occurred frequently in this group of cases, the degree apparently bearing some relation to the severity of the disease. The following averages were obtained. In six mild cases, 16.9 mg. per hundred of blood; in twenty-five moderately severe cases, 21.87 mg., and in eleven very severe cases, 25.7 mg. (Table 2). The findings in relation to the day of the disease are given in Table 4. The average in four cases on the first day of the disease amounting to 16.03 mg. per hundred c.c. of blood. The figures for urea parallel those for urea nitrogen.

TABLE 2.—BLOOD CHEMISTRY FINDINGS IN RELATION TO THE SEVERITY OF THE DISEASE

Clinical Type of the Disease	Number of Cases	Chlorids Average, Per Cent.	Creatinin Average Mg. per 100 C.c. of Blood	Urea Nitrogen Average Mg. per 100 C.c. of Blood	Uric Acid Average Mg. per 100 C.c. of Blood
Mild..................	8	0.62	1.06	16.9	3.75
Moderately severe....	24	0.60	1.58	21.92	3.75
Very severe and fatal cases............	26	0.56[1]	1.49	25.17	4.98[2]

1. Average for 24 cases.
2. Average for 20 cases.

Uric acid being the most difficult of the nitrogenous waste products for the kidneys to eliminate, it might be expected to be found increased in the blood, under certain circumstances, even when the urea and creatinin are normal. In the group of cases under discussion an increase of blood uric acid was frequently encountered. As a rule, this increase was proportional to the severity of the disease. In eight mild cases an average of 3.5 mg. per hundred c.c. of blood was found; in twenty-four moderately severe cases 3.75 mg., and in twenty very severe cases it was increased to 4.98 mg. (Table 2). The highest findings for uric acid were on the third day of the disease, the lowest on the fourth and fifth days (Table 3). The highest figure for uric acid encountered in this series was in Case 10 (Table 1), a moderately severe case, with 18.1 mg. per hundred c.c. of blood.

The blood of sixteen fatal cases was examined on various days of the disease (Table 4). In these cases a greater reduction in the urinary chlorids was found. In general, the blood chlorids and sugar were normal. Urea and urea nitrogen were usually increased. In cases 4, 10 and 15, in which the determinations were made one and

two days before death, these products were decidedly increased. Uric acid was increased in practically every case, averaging 4.46 mg. per hundred c.c. of blood. In this group of cases such factors as the day of the disease, duration and complications had little influence on the degree of retention.

The original plan of this investigation was twofold: to study the retention of the nitrogenous waste products in the blood of pneumonia cases uninfluenced by any special form of treatment, and to determine any possible alteration in the degree of retention resulting from the intravenous injections of foreign protein and hypertonic glucose solutions. In the reaction which frequently follows the intravenous injection of a foreign protein profuse sweating occurs; that this reaction might have a modifying effect upon the degree of retention seemed possible, especially in view of the marked improvement which frequently followed such injections.

TABLE 3.—BLOOD CHEMISTRY FINDINGS IN RELATION TO THE
DAY OF THE DISEASE

Day of the Disease	Number of Cases	Chlorids Average, Per Cent.	Creatinin Average Mg. per 100 C.c. of Blood	Urea Nitrogen Average Mg. per 100 C.c. of Blood	Uric Acid Average Mg. per 100 C.c. of Blood
First................	4	0.51	1.94	16.03	4.59[1]
Second...............	16	0.64	1.62	19.85	4.53[2]
Third................	9	0.52	1.54	21.16	6.06
Fourth...............	5	0.58	1.22	23.54	3.02
Fifth................	9	0.56	1.06	22.14	3.11

1. Includes 5 cases.
2. Includes 17 cases.

Thirteen cases of pneumonia are cited in which one or more blood chemistry determinations were made before and after the intravenous injection of a hypertonic glucose solution, including a total of sixty-three determinations (Table 5). The results in these cases were not as striking as we had hoped. It was thought possible that an appreciable reduction might occur following the injection of large quantities of glucose solution. There was a slight reduction of urea nitrogen and urea in Case 3. In Case 4, uric acid was reduced on the second day, creatinin on the third day, and urea and urea nitrogen on the fifth and seventh days; on the second day, however, the latter product was slightly increased. In Case 8, on the third day uric acid was reduced from 6.4 to 2.5 mg. per hundred c.c. of blood four hours after the injection of 250 c.c. of glucose solution. In Case 10, on the sixth day there was an appreciable reduction in urea five hours after the injection of the glucose. In Case 3, on the second day urea nitrogen, urea and uric acid were slightly increased four hours after the injection. In Case 6, on the third day the uric acid doubled in

amount two hours after the injection. In Case 8 urea was increased on the third day, and on the sixth day uric acid was greatly increased, three and eighteen hours after the injection.

Six cases are included in the foreign protein group (Table 5). Only two of these permitted satisfactory chemical examinations of the blood with reference to the injection of the protein. In Case 5, four hours after the injection of 0.5 c.c. of a typhoid vaccine, sufficient to cause a moderate reaction, there occurred a moderate reduction in all the nitrogenous waste products in the blood. In Case 6, there occurred on the first day a considerable increase in the uric acid content of the blood four hours after the intravenous injection of the protein. In three cases in this group uric acid retention was found present following the injections.

TABLE 4.—BLOOD CHEMISTRY DETERMINATIONS IN FATAL CASES OF INFLUENZAL PNEUMONIA

| Case Number | Urine | | | | | Blood Chemistry Findings | | | | | | | | Day of Death |
| | Albumin | Casts | 24 Hour Specimen | | | Day of Disease | Chlorids, per Cent. | Sugar, per Cent. | Creatinin, per 100 Blood, Mg. C.c. | Urea Nitrogen, Mg. per 100 C.c. Blood | Urea, Mg. per 100 C.c. Blood | Uric Acid, per 100 Blood, Mg. C.c. | CO2 Combining Power of the Blood Plasma | |
			Day of Disease	Chlorids, Gm.	Urea, Gm.									
1	P	P	..	...	....	1	0.69	0.14	1.0	18.2	38.94	1.51	57	7th
2	N	N	3	...	19.0	2	0.63	0.16	1.7	21.3	45.58	...	54	3d
3	P	P	6	8.0	38.0	2	0.64	0.16	1.5	22.1	47.29	2.2	58	10th
4	N	N	..	...	....	2	0.42	0.14	1.1	27.25	58.31	8.8	..	4th
5*	P	P	3	1.3	....	2	0.69	0.13	1.01	20.7	44.29	3.65	51	18th
6	N	N	..	...	....	3	0.48	0.15	1.85	28.5	60.95	6.0	..	6th
7	P	N	..	...	....	4	0.53	0.11	0.9	27.75	59.28	2.5	..	4th
8	P	N	3	1.0	....	5	0.63	0.12	0.9	16.3	34.88	3.15	54	11th
9*	N	N	..	...	....	5	0.58	0.15	0.9	19.0	40.60	...	..	6th
10	N	N	..	...	....	5	....	0.14	1.4	44.1	94.37	...	..	7th
11	N	P	..	...	....	6	....	0.15	1.05	21.3	45.58	...	..	7th
12	P	N	3	1.0	....	6	0.63	0.13	1.05	31.2	66.76	5.0	52	11th
13*	N	N	..	...	....	7	0.56	0.15	1.5	19.0	40.66	T	44	9th
14	N	N	..	...	....	7	0.5	0.16	1.5	19.2	41.08	...	..	8th
15	N	N	..	...	....	7	0.58	0.18	1.55	34.1	72.97	3.9	..	8th
16	..	..	10	1.3	....	9	0.71	0.15	1.1	27.5	58.85	7.9	..	19th

* Cases in which pleurisy or empyema occurred.

Case 8 (Table 5) is sufficiently unusual to merit some discussion. A graphic presentation of the retention curve for the various nitrogenous waste products is given in the accompanying chart. This case was of the type in which clinical experience had taught us to expect a fatal termination. The patient was delirious and irrational for several days, presented marked cyanosis and dyspnea, rapid and thready pulse, and high fever. On the ninth day of the disease, the blood chemistry findings were, creatinin, 5.1 mg.; urea nitrogen, 148.0 mg.; urea, 315.7 mg. and uric acid, 9.6 mg. per hundred c.c. of blood. An acute kidney involvement was present but cleared rapidly with convalescence. In Case 4 of the glucose series an equally severe clinical

TABLE 5.—BLOOD CHEMISTRY BEFORE AND AFTER THE INTRAVENOUS ADMINISTRATION OF GLUCOSE SOLUTION AND FOREIGN PROTEIN

Case Number	Albumin	Casts	Urine 24 Hr. Spec. Day of Disease	Urine Chlorids, Gm.	Urine Urea, Gm.	Before: Day of Disease	Before: Hours Before Injection	Before: Chlorids, per Cent.	Before: Sugar, per Cent.	Before: Creatinin, Mg. per 100 C.c. Blood	Before: Urea Nitrogen, Mg. per 100 C.c. Blood	Before: Urea, Mg. per 100 C.c. Blood	Before: Uric Acid, Mg. per 100 C.c. Blood	Before: CO₂ Combining Power of the Blood Plasma	After: Day of Disease	After: Hours After the Injection	After: Chlorids, per Cent.	After: Sugar, per Cent.	After: Creatinin, Mg. per 100 C.c. Blood	After: Urea Nitrogen, Mg. per 100 C.c. Blood	After: Urea, Mg. per 100 C.c. Blood	After: Uric Acid, Mg. per 100 C.c. Blood	After: CO₂ Combining Power of the Blood Plasma	Number of C.c. of Glucose Injected	Remarks
1	N	N	:	:	19.0	2	6	0.68	0.15	1.7	21.3	45.58	:	54	4 / 5	24 / 1	0.57 / 0.58	0.20 / 0.26	1.5 / 2.55	22.1 / 41.2	47.29 / 87.95	2.2 / 2.42	58 / 52	800	Severe case with death, showing no reduction in retention
2	N	N	3	1.7	...	2	1	0.74	0.12	0.85	18.0	38.52	2.2	:	3	22	0.68	0.11	0.75	16.2	34.66	3.45	:	250	Moderately severe case, showing slight reduction
3	N	N	.	...	...	2 / 3	2 / 1	0.51 / 0.45	0.09 / 0.09	1.1 / 1.05	16.3 / 19.0	34.88 / 40.8	1.2 / 1.21	:	2 / 3	4 / 6	0.50 / 0.53	0.11 / 0.13	1.1 / 1.05	18.0 / 18.2	38.52 / 38.94	1.31 / 1.3	:	250	Moderately severe, showing slight reduction
4	P	P	19	12.4	40.85	2 / 3 / 4 / 5 / 6 / 7	1 / 1 / 1 / ¼ / 1 / ¾	... / 0.56 / 0.51 / 0.53 / 0.55 / 0.50	0.11 / 0.12 / 0.11 / 0.12 / 0.13 / 0.13	1.6 / 2.85 / 2.4 / 1.85 / 1.75 / 1.1	22.27 / 26.5 / 25.0 / 20.25 / 18.0 / 15.3	47.65 / 55.71 / 53.5 / 43.33 / 38.52 / 32.74	6.6 / 4.4 / ... / 3.05 / ... / 1.98	:	2 / 3 / 4 / 5 / 6 / 7 / 8 / 10 / 11 / 32 / 50	4 / 6 / 6 / 5 / 5 / 18 / 68 / 80 / : / :	... / 0.54 / 0.52 / 0.50 / 0.52 / 0.49 / 0.51 / 0.55 / 0.53 / 0.52 / 0.49	0.15 / 0.12 / 0.12 / 0.12 / 0.11 / 0.11 / 0.11 / 0.10 / 0.09 / 0.15	1.7 / 2.1 / 1.85 / 1.75 / 1.05 / 1.0 / 0.70 / 1.0 / 1.1 / 1.0 / 1.7 / 0.55 / 0.9	23.75 / 26.0 / 22.0 / 19.2 / 17.5 / 13.6 / 12.0 / 13.0 / 18.0 / 12.0 / 10.6	50.825 / 55.6 / 41.08 / 41.08 / 37.45 / 29.104 / 26.68 / 27.82 / 38.52 / 25.68 / 20.084	5.7 / 6.1 / ... / 3.85 / 2.25 / 1.80 / 1.21 / 1.0 / 1.725 / 0.82 / 1.48	:	250 / 250 / 250 / 220 / 250 / 350	Very severe case, slight uric acid reduction, after first injection. Recovery was very slow
5*	P	P	:	:	...	1	6	0.56	0.15	1.55	19.3	41.30	12.1	:	4	24	0.60	0.15	1.9	30.0	64.2	4.8	:	250	Recovery
6	P	P	6	8.0	38.0	2 / 3	24 / 9	0.64 / 0.60	0.16 / 0.13	1.5 / 1.05	22.1 / 20.0	47.29 / 42.8	2.2 / 1.61	58 / 49	3 / 4 / 5	2 / 18 / 48	0.54 / 0.49 / 0.71	0.16 / 0.15 / 0.15	1.25 / 1.6 / 2.10	20.1 / 19.5 / 35.2	43.01 / 41.73 / 75.32	3.7 / 2.0 / 2.75	... / 55 / 38	250 / 500 / 500	Mild case. Severe case with death. Shows increased retention and decrease of CO₂ combining power of blood plasma
7	N	N	:	:	...	3 / 6	7 / 12	0.48 / 0.47	0.15 / 0.17	1.85 / 2.2	28.5 / 99.0	60.95 / 211.86	6.0 / 8.8	:	: / :	: / :	:	:	:	:	:	:	:	250 / 500	Severe case with death

No.								Before Foreign Protein Injection								After Foreign Protein Injection									Dose	Remarks
8	P	P	12, 16	3.0, 1.5	29.07, 31.0	3, 4, 6	2, 7, 4	…	0.44, 0.49, 0.44	0.13, 0.13, 0.12	1.0, 1.5, 0.9	20.75, 24.25, 32.75	44.4, 51.895, 70.085	6.4, 3.1, 3.5	…	3, 5, 6, 6, 6, 7, 8, 9, 10, 11, 14, 20, 23	4, 15, 3, 18, 26	0.46, 0.44, 0.48, 0.51, 0.51, 0.51, 0.50, 0.52, 0.51, 0.47, 0.57, 0.67	0.16, 0.16, 0.16, 0.14, 0.15, 0.14, 0.14, 0.13, 0.11, 0.15, 0.21, 0.10, 0.11	1.4, 0.9, 2.5, 3.1, 4.0, 2.2, 2.8, 5.1, 5.0, 2.7, 1.5, 0.9, 1.2	25.5, 32.75, 32.25, 81.0, 83.5, 114.0, 106.0, 148.0, 85.0, 61.0, 36.0, 16.3	54.57, 70.085, 69.01, 173.34, 179.69, 243.9, 226.8, 315.7, 181.9, 130.54, 77.0, 34.88	2.5, 3.5, 3.5, 7.2, 9.2, 10.0, 10.4, 10.6, 11.8, 9.6, 6.7, 5.4, 1.28	…	250, 250, 250	Unusually severe, with recovery / Showing high degree retention / Glucose per rectum (×10)
9	N	N	2	1.2	…	2	72	55	0.61	0.14	3.05	19.5	41.73	4.07		4	22	0.59	0.17	1.85	23.7	50.71	3.15	…	275, 250	Moderately severe, with recov. / Showing slight reduction
10	N	N	…	…	…	5, 6	1, 1	…	0.54, 0.46	0.09, 0.10	0.55, 1.1	16.75, 15.25	35.84, 32.63	0.66, 1.42		6, 7	5, 24	0.50, 0.49	0.11, 0.10	1.25, 1.1	14.0, 11.5	29.96, 24.6	1.97, 2.2	…	250	Moderately severe, with recov. / Showing slight reduction
11	P	N	…	…	…	4	1	…	0.53	0.11	0.9	27.75	59.285	2.5		4	4	0.45	0.09	0.9	27.5	58.85	2.65	…	250	Very severe, with death
12	N	N	…	…	…	7	6	…	0.50	0.16	1.5	19.2	41.08	…		9	24	0.56	0.13	0.9	19.5	41.73	…	…	650	Very severe, with death
13*	N	N	15	1.3	…	15	1	…	0.71	0.15	1.1	27.5	58.85	7.9		15	22	0.63	0.13	0.9	23.7	50.71	5.7	51	500	Very severe, with death
1	N	N	3	1.2	…	…	…	…	…	…	…	…	…	…		2	24	0.80	0.11	1.35	18.2	38.94	3.92	51	…	Moderately severe, recovery
2	N	N	…	…	…	…	…	…	…	…	…	…	…	…		1	3	0.58	0.17	1.1	16.7	35.7	2.65	…	…	Moderately severe, recovery
3	P	P	6	8.0	38.0	2, 3	½, 7	58, 49	0.64, 0.60	0.16, 0.13	1.5, 1.05	22.1, 20.0	47.29, 42.80	2.2, 1.61		…	…	…	…	…	…	…	…	…	…	Very severe, with death
4	P	P	3	1.0	…	…	1	48	…	…	…	…	…	…		3	24	0.63	0.12	0.9	16.3	34.88	3.15	54	…	Very severe, with death
5	P	P	…	…	…	1	1	48	0.60	0.16	2.10	17.2	36.8	6.1		1	4	0.61	0.15	2.05	16.3	34.88	5.0	…	…	Very severe, with recovery
6	P	P	…	…	…	1, 3	½, ¼	57, 57	0.69, 0.55	0.14, 0.14	1.0, 1.0	18.2, 12.0	38.94, 25.69	1.51		1, 3	4, 24	0.60, 0.54	0.12, 0.24	1.75, 3.4	18.0, 12.0	38.52, 25.68	4.0	46, 47	…	Very severe, with death

* Cases in which pleurisy or empyema occurred.

picture was presented with slightly less retention. Case 7, terminating fatally, also presented marked retention (Table 5).

COMMENT

The literature dealing with blood chemistry findings in pneumonia is limited, and the reports available are inconclusive as to their value in this disease. Gettler [1] explains the retention of nitrogenous products in the blood to an accompanying renal involvement, stating,
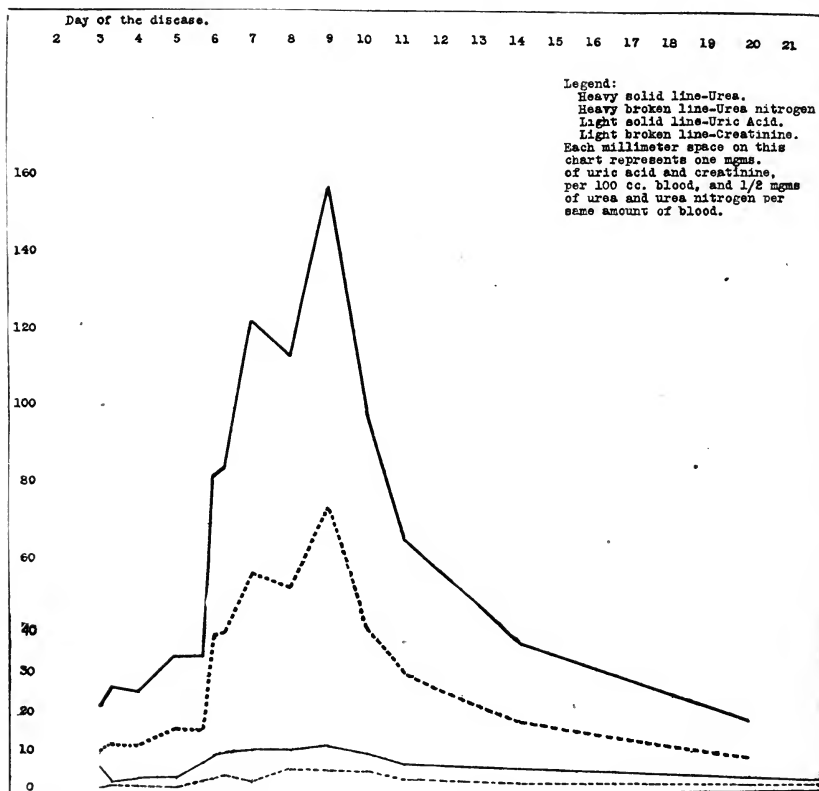
Blood Chemistry Findings in Case 8, Table 5.

"we can safely assume, therefore, that the complicating nephritis was the chief cause of the retention, and not pneumonia." Matz [3] claims the retention is due to "protein injury, disintegration and autolysis accompanying excessive lung inflammation." Both writers are undoubtedly correct, but other factors may also be contributory; particularly, impairment of the circulatory function, as found in cases with extreme cyanosis and rapid pulse. Nor need the protein injury be confined to the pulmonary inflammation, for other tissues of the

3. Am. J. M. Sc., **158**: 723 (Nov.), 1919.

body may be subject to more than normal insult and catabolic changes, with a resulting increase in the nitrogenous waste products. The influence of diet as a factor furthering retention may be eliminated from this study, since all these patients were on liquid diet during the period of the blood examinations.

Tileston and Comfort[4] report fourteen cases of pneumonia in which blood urea determinations were made; finding 36.0 mg. per hundred c.c. of blood as the highest retention, and 11.2 mg. as the lowest. They conclude that there is no relation between retention and prognosis. Schwartz and McGill[5] report forty-four case determinations of blood urea in pneumonia, finding as their highest 104.4 mg., and their lowest 12.0 mg. per hundred c.c. of blood. Thirty-six of their determinations were above normal. Some of the patients were cyanotic at the time the blood was obtained. Seventeen had a definite toxic nephritis; and it was to the latter they attributed this increase. Only one of their cases having blood urea over 60.0 mg. per hundred c.c. of blood recovered. They therefore concluded that cases with marked retention offer a bad prognosis. They noted that the maximum retention occurred about the time of crisis in the lobar type of pneumonia, although in several it occurred on the first and second days of the disease. Foster[6] states that uric acid has been consistently found increased in pneumonia, but that in his experience an increase in the nonprotein nitrogen has been exceptional and associated with marked evidence of circulatory disturbance. Gettler and St. George[7] found little or no chlorid retention in the blood of pneumonia cases. Meyers and Lough[2] claim that the retention of creatinin practically only occurs in cases having an associated renal involvement, and that values of 5.0 mg. or more per hundred c.c. of blood indicate a fatal termination; and that values for urea nitrogen of 40.0 mg. or more indicate a bad prognosis.

In most of the fatal cases in this study an increase in blood uric acid was shown (Cases 4, 6 and 16, Table 4; Cases 7 and 13, Table 5; Cases 10, 19 and 20, Table 1, and two nonfatal cases, 4 and 8, Table 5). The average uric acid found in thirty-nine nonfatal cases was 3.14 mg. per hundred c.c. of blood, while in ten fatal cases the average was 4.45 mg. Four cases in this series had uric acid values over 10.0 mg. All these patients recovered. Uric acid is stated to to be the first of the nitrogenous waste products retained and the most difficult to eliminate. Creatinin, on the other hand, is the most readily eliminated and the last retained (Meyers and Lough).[2] The serious significance of the retention of over 5.0 mg. of creatinin per

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4. Arch. Int. Med., **14**:620 (Nov.) 1914.
5. Arch. Int. Med., **17**:42, (Jan.) 1916.
6. Arch. Int. Med., **15**:356, (March) 1915.
7. J. A. M. A., **71**:2053, (Dec. 21), 1918.

hundred c.c. of blood has been cited above. Case 8 (Table 5) is a case of this character. It also gave findings of 148. mg. of urea nitrogen, yet recovery occurred. Seven of the nonfatal cases, and three of the fatal cases gave findings of urea nitrogen over 40.0 mg. per hundred c.c. of blood.

The carbon dioxid combining power of the blood plasma in cases of pneumonia has not been dealt with in this paper, although a few such readings have been included in the tables. From the few cases examined in this respect, the conclusion is warranted that a lowering of the carbon dioxid combining power of the blood plasma is very apt to be found in patients seriously ill, and particularly when there is also extensive pulmonary involvement or marked circulatory disturbance.

No conclusions relative to the effect of the crisis in pneumonia on the degree of retention can be drawn from this study, since the majority of the cases terminated by lysis.

The relation of the day of the disease to the degree of retention is shown in Table 2. At no time was there found an increase in the chlorids, although the urinary chlorids were greatly diminished. Creatinin appeared to be slightly increased on the first day of the disease. This might be construed as contrary to the conclusions of Meyers and Fine that creatinin is the last of the nitrogenous products to be retained. The increase in our cases is too small to warrant definite conclusions in this regard. Urea nitrogen and urea retention were most marked on the third and fourth days of the disease. The highest average figures for uric acid occurred on the third day. The two latter findings were to be expected.

A very definite relation is evident between the severity of the disease and the degree of retention of urea nitrogen, urea, uric acid and to a lesser degree creatinin (Table 3). The occurrence of empyema and pleurisy had little or no influence on the findings in this series.

Among the students of blood chemistry there seems to be a tendency to minimize its value when applied to cases of pneumonia. Certainly as far as reported studies are concerned, such conclusions are not warranted, especially in view of the few observations on record. Before the value of the application of blood chemistry studies to pneumonia can be decided, there is need for more extensive application of its use in these cases. These studies should take into consideration such factors as diet, drug therapy, serum therapy, kidney function, extent of lung involvement, type of infection, etiologically and pathologically; the condition of the circulatory apparatus, presence of complications, and the severity of the disease. I do not care to draw more definite conclusions in this regard than have been intimated, leaving such for a more intensive study.

BLOOD CHEMISTRY OF PERNICIOUS ANEMIA *

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AND

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Kahn and Barsky [1] recently published an admirable paper in which they report the results of the blood analyses and the functional capacity of the various organs in three cases of pernicious anemia. Their study revealed the following conditions:

Stomach: Gastric stasis seemed to be present; free acid and pepsin absent. The mucosa appeared to be nonfunctioning, the result of atrophy.

Intestines: Digestion and absorption, especially that of the proteins, were disturbed and below normal. Intestinal putrefaction was increased.

Pancreas: The pancreatic enzymes were present in normal amounts and tests showed that the pancreas was functioning normally.

Liver: The function of detoxication was deficient. Other functions, such as the glycogenic, ureogenic, biligenic, were normal.

Pigments: Both pleochromie and urobilinocholia existed, showing that excessive hemolysis was going on.

Kidneys: The excretory function of the kidneys was normal.

Urine: Quantitative partition nitrogen determinations proved the normal output of the excretory nitrogenous substances with the exception of a greatly increased oxyproteic acid.

Blood: The nonprotein nitrogen, urea and uric acid content was normal. The creatinin was increased. The glucose, fat, and cholesterol were normal. The alkaline reserve was below normal, showing an acidosis. The specific gravity of the plasma was lowered and the protein content was much reduced. The ash and calcium were slightly increased.

The work reported in the present paper deals solely with the analysis of the blood. The work was started in 1916. Thirty-two cases have been studied. In most of the cases several complete blood analyses were made at intervals of a month or more. In Case 1,

1. Kahn, M., and Barsky, J.: Arch. Int. Med. **23**: 334 (March 1919.

TABLE 1.—RESULTS OF ANALYSES OF BLOOD IN PERNICIOUS ANEMIA

Case	Sex	Months Between Transfusions	Nonprotein Nitrogen	Urea Nitrogen	Amino-acid Nitrogen‡	Uric Acid	Creatinin	Sugar	Per Cent. Alkaline Reserve	Refraction *	Specific Gravity	Freezing Point	Erythrocytes	Hemoglobin, Sahli, per Cent.	Total Volume of Blood
1	M	0	34	12	12	7.5	1.1	125	52	15.3	1.0250	0.550			
		2	59	24	23	8.2	1.5	115	56	14.8	1.0245	0.560			
		2	46	15	20	6.2	1.9	192	50	15.2	1.0261	0.550			
		1	38	12	17	2.6	1.9	90	56	14.1	1.0230	0.562	2,220,000	44	2,159
		1	43	16	16	4.8	2.1	105	52	13.3	1.0245	0.568	2,800,000	54	2,965
		7	37	10	17	4.0	1.7	77	58	13.6	1.0225	0.610	2,510,000	48	1,800
		1	47	17	20	3.8	2.0	80	55	12.5	1.0200	0.625	2,580,000	48	2,200
		1	49	18	20	2.6	1.9	111	47	12.0	1.0205	0.585	2,410,000	46	2,330
2	M	0	32	10	14	2.5	1.1	154	34	15.1	1.0215	0.630	3,040,000	60	3,585
		3	41	15	15	3.1	1.6	131	39	14.7	1.0220	0.625	1,800,000	35	3,502
		4	40	12	16	6.0	1.1	136	48	14.9	1.0210	0.615			
		2	36	11	15	5.0	0.8	300	56	14.8	1.0270	0.690			
		2	45	17	17	3.6	1.8	121	60	12.6	1.0200	0.582			
		1	33	10	12	4.7	1.6	118	53	11.8	1.0190	0.580			
3	F	0	37	12	13	2.8	1.9	98	44	16.1	1.0265	0.610	1,000,000	22	2,147
4	M	0	35	11	11	7.5	1.9	125	50	14.2	1.0235	0.595			
5	M	0	36	12	13	5.0	1.9	105	46	14.8	1.0195	0.630			
6†	F	0	30	9	10	4.4	1.7	128	42	15.7	1.0229	0.625	1,080,000	25	2,004
		2	37	11	13	4.1	1.4	120	48						
7	M	0	27	9	11	3.1	1.8	96	33	15.5	1.0265	0.615			
8	M	0	24	9	9	8.0	1.3	100	45	16.0	1.0255	0.635			
		2	37	12	18	5.1	1.5	133	46	15.7	1.0240	0.650			
		5	42	17	16	5.9	1.8	133	50	15.2	1.0240	0.610			
		2	37	13	16	3.3	1.7	82	42	15.7	1.0255	0.620			
		¼	65	29	25	3.1	2.1	101	55	16.8	1.0230	0.605	1,180,000	25	2,260
		6	108	75	24	8.5	3.1	176	54	15.3	1.0245	0.600	1,520,000	30	2,277
		1	65	27	26	6.3	2.8	130	55	13.5	1.0240	0.685			
		1	48	19	20	4.0	1.9	128	35	12.2	1.0200	0.648			
9	F	0	34	9	17	4.5	1.3	125	55	16.8	1.0270	0.615	....	..	1,800
		⅓	49	20	21	4.3	0.9	91	50	16.1	1.0265	0.625			
		1	65	34	21	4.7	0.3	111	48	16.4	1.0270	0.633			
		1	33	8	17	5.0	0.6	95	60	16.4	1.0280	0.612			
		1	34	11	15	3.7	1.1	115	53	16.0	1.0250	0.589			
10	M	0	30	12	9	4.5	0.6	136	38	15.5	1.0220	0.590	780,000	18	2,200
		2	33	11	12	2.5	0.8	125	52	15.8	1.0236	0.575			
		2	39	15	17	3.9	1.1	130	50	14.3	1.0227	0.549			
		1	36	14	12	5.0	1.0	129	42	11.7	1.0170	0.546			
11	M	0	47	15	22	7.0	1.3	107	54	13.5	1.0215	0.655			
		1	44	16	21	5.5	1.2	115	60	11.8	1.0215	0.557			
		1	73	40	29	10.0	1.1	120	48	11.3	1.0166	0.555			
12	F	0	55	26	21	4.0	2.1	106	50	14.4	1.0240	0.759	1,482,000	30	2,878
13	F	0	31	8	15	1.7	1.1	86	55	15.1	1.0225	0.595			
		5	35	9	18	2.5	1.3	90	63	14.6	1.0215	0.578	2,850,000	61	8,887
14	M	0	45	16	21	5.1	1.7	131	65	16.3	1.0260	0.600	1,700,000	34	2,560
		12	35	10	17	7.5	1.9	113	50	16.0	1.02595	0.590	2,040,000	39	2,866
		8	69	38	24	5.8	1.1	125	54	15.8	1.0266	0.595	1,710,000	32	2,679
		2	46	18	18	3.3	1.2	111	58	16.9	1.0264	0.580			
15	M	0	30	8	13	3.3	1.0	112	52	14.0	1.0220	0.628	1,220,000	26	
		1	35	10	17	4.1	1.5	118	50	13.6	1.0250	0.620	990,000	23	1,500
		6	40	12	18	4.5	1.0	145	50	12.8	1.0200	0.570			
		3	37	9	18	3.5	0.8	120	49	12.8	1.0191	0.615			
16	F	0	39	14	18	5.0	1.3	136	58	14.8	1.0225	0.592			
		3	46	15	20	3.7	1.5	119	53	13.0	1.0210	0.570			
17	M	0	42	13	19	1.1	0.5	79	52	17.1	1.0275	0.610	1,800,000	38	3,323
18	M	0	47	15	24	4.4	2.7	94	53	15.5	1.0256	0.595	....	..	1,870
		1	46	17	20	2.3	1.3	94	72	14.9	1.0274	0.615	....	..	2,302
		1	60	28	23	4.0	1.7	70	66	15.9	1.0278	0.624	....	..	2,325
19	M	0	62	29	15	3.7	1.4	80	56	16.6	1.0266	0.580	1,800,000	34	1,688
		3	41	14	19	4.6	2.1	80	50	16.1	1.0259	0.610	1,410,000	28	1,340
		9	39	14	20	2.0	0.6	92	56	14.8	1.0255	0.610	1,000,000	22	2,680
20	F	0	57	25	21	5.0	0.4	103	68	14.1	1.0290	0.588			
		5	38	11	19	3.5	0.6	103	63	13.8	1.0275	0.587			
21	M	0	41	14	20	4.3	1.8	150	44	15.9	1.0248	0.610			
		3	50	19	22	8.6	1.6	187	52	14.8	1.0228	0.635			
		2	32	10	13	7.6	1.7	160	42	15.1	1.0230	0.595	1,300,000	27	3,938
		15	78	47	22	7.0	2.1	128	53	12.0	1.0200	0.607			
		½	59	32	21	7.9	1.9	130	56	13.3	1.0200	0.620			
		1	67	35	23	9.9	2.2	140	55	12.8	1.0199	0.596			

* △ Nd × 10³
† Spleen removed six months previous to first analysis.
‡ D. D. Van Slyke's method was used.

TABLE 1.—Results of Analyses of Blood in Pernicious
Anemia—(*Continued*)

Case	Sex	Months Between Transfusions	Mg. in 100 C.c. of Blood						Per Cent. Alka-line Reserve	line Reserve Refraction	Specific Gravity	Freezing Point	Erythrocytes	Hemoglobin, Sahil, per Cent.	Total Volume of Blood
			Nonprotein Nitrogen	Urea Nitrogen	Amino-acid Nitrogen	Uric Acid	Creatinin	Sugar							
22	M	0	42	16	15	2.8	1.1	102	59	12.7	1.0200	0.607			
23	M	0	44	16	16	2.1	1.2	175	62	17.0	1.0260	0.579			
24	F	0	40	15	18	5.3	1.5	120	62	15.3	1.0230	0.592			
25	M	0	59	25	24	10.0	1.2	142	46	15.7	1.0221	0.585	820,000	17	1,900
		3	34	9	15	7.2	1.5	121	58	16.2	1.0239	0.710			
		2	38	9	20	6.0	0.9	109	61	15.7	1.0205	0.565			
26	M	0	61	30	23	1.8	1.5	125	53	16.8	1.0285	0.610			
		2	33	10	13	0.8	0.8	81	66	17.1	1.0271	0.615			
		2	33	11	15	1.0	1.0	176	51	16.9	1.0275	0.595	2,300,000	50	3,100
27	M	0	33	9	17	3.9	1.4	126	65	15.9	1.0258	0.625			
28	M	0	30	11	12	4.4	1.9	187	53	15.6	1.0257	0.635			
		2	43	20	15	2.9	1.4	132	50	16.1	1.0269	0.628	....	..	4,200
29‡	M	0	44	16	20	3.4	1.3	120	60	16.1	1.0238	0.588			
		8	37	15	15	3.0	1.1	158	70	16.7	1.0342	0.583	980,000	20	2,120
		4	39	15	18	4.3	1.5	166	36						
		4	42	17	16	5.5	0.9	94	52						
30	F	0	37	10	19	3.3	2.1	125	50	15.4	1.0333	0.624			
31	F	0	36	12	15	6.9	1.5	125	46	13.4	1.0226	0.579	700,000	16	2,689
32	M	0	66	40	18	7.1	2.1	181	58	12.9	1.0256	0.605	1,100,000	20	2,170

‡ Spleen removed one year before first analysis.

eight such analyses were performed within a period of fifteen months. In all, the thirty-two cases yielded eighty-seven complete analyses. The methods were the same as those used in the analysis of normal cases.[2]

Nonprotein Nitrogen: Although 52 per cent. of the cases are within the normal limits of nonprotein nitrogen (from 25 to 40 mg.), the remaining 48 per cent., an amount too large to be accidental, shows values above the normal limit. They range principally between 40 and 60 mg. Twelve of the cases (14 per cent.) have a value of above 60 mg.

Urea Nitrogen: Among the values for urea nitrogen, only 18 per cent. are above the normal, the remainder being within the normal limits (10 to 20 mg.), but even in these the tendency toward the higher normal limit is noticeable.

Amino-Acid Nitrogen: The nitrogen found in this form is higher than the normal in practically all the cases. In some of the cases the amount is as much as four times that of the normal.

Uric Acid: Of all the nonprotein nitrogenous excretory products, it is the uric acid that shows the greatest rise. Ninety per cent. of the cases have a uric acid value that is higher than normal (from 0.5 to 3.0 mg). In 38 per cent of the cases the values are above 5 mg., many of them showing values as high as 9 and 10 mg.

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2. Gettler, A. O., and Baker, W.: J. Biol. Chem. **25**: 211, 1916.

Creatinin: Fifty-eight per cent. of the values are within the normal limits (from 0.1 to 1.5 mg.). The remaining 42 per cent. have higher values, but the creatinin rarely rises higher than 3 mg. In our series only one case was found above (3.1 mg.).

The above values for the nonprotein nitrogenous substances indicate that the kidney function is slightly impaired. This is apparently not due to a permanent lesion of the kidney, but to the fact that much less blood circulates because of the anemic condition. The increased nonprotein nitrogen figures must not be taken as a direct measure of kidney function in these cases of pernicious anemia, because only part of this rise is due to the lessened activity of the kidneys. Another and equally important cause for this rise in nonprotein nitrogen is the presence in the circulation of an abnormally high amino-acid content.

For the presence of the increased amino-acid content in the blood several theories may be given:

1. The organism has lost the power to synthetize serum proteins.

2. It is decomposing serum proteins at an abnormally high rate.

3. The muscles and organs are not absorbing amino-acids as they do under normal conditions.

4. The muscles and organs, especially the liver, have lost their deamidizing power.

5. The protoplasm of the cells is being broken down into its constituent amino-acids.

6. Oxidation throughout the organism has been greatly reduced, thus giving rise to a large quantity of oxyproteic acid which, owing to its free amino groups, will react in the Van Slyke estimation of amino-acids and thus give high results.

These six theories are simply put forth as possibilities which future research may prove or disprove. At this stage, however, it seems likely that the abnormally high values of amino-acid are due partly to the fact that increased amounts of oxyproteic acid are being produced in this disease, but principally to the abnormally large destruction of serum proteins and their hydrolysis to amino-acids.

The uric acid rise is out of all proportion to the other nonprotein nitrogenous constituents.

Sugar: Seventy per cent. of the cases show a blood sugar value above normal (from 60 to 100 mg.), 19 per cent. being above 130 mg. This indicates either that the body is not oxidizing the sugar as fast as it should, or that the glycogen-glucose equilibrium has been disturbed. The more probable explanation is the first one. The oxidizing processes of the cells are evidently at a lower level than under normal conditions.

Alkaline Reserve: This is diminished in practically all pernicious anemia cases. In our series, 50 per cent. are below the normal values (from 53 to 75 per cent.), the lowest value obtained being 33 per cent. The remaining 50 per cent., although within the normal limits, show a tendency toward low values, as indicated by the fact that only 14 per cent. of the cases show values above 60 per cent.

The reason for this lowering of the alkaline reserve (production of acidosis) in pernicious anemia appears to be the result of diminished oxidation. In this way, organic acids that normally would be oxidized to carbon dioxid and water are not destroyed, but, instead, are partly neutralized by the fixed bases and eliminated as such. In this way alkali is continually lost to the organism and the low alkali reserve results.

Physical Constants: The refraction brings out the interesting fact that in the blood of pernicious anemia patients the serum proteins are greatly reduced. In our series, 76 per cent. are below the normal value (from 16 to 18). In many of these cases we find the serum protein lower than in cases of severe nephritis with edema. The decrease in serum protein may be as much as from 40 to 50 per cent. of the amount of normal serum.

Specific Gravity: The specific gravity runs parallel with the refraction. Eighty per cent. of our cases show values below the normal (from 1.0270 to 1.0295). This is to be expected as the decrease in protein content affects the specific gravity in the same direction as it does the refraction.

Freezing Point: The least variation from the normal (from 0.520 to 0.610) is found in the freezing point. Here only 28 per cent. of the cases are above the normal values. Among those that show values within the normal limits, there is also seen this tendency toward a rise, but it is not enough to bring it above the accepted normal limit. The cause for this small increase in freezing point is twofold: first, the increased nonprotein nitrogenous substances, and, secondly, the fact, as shown by Kahn and Barsky, that the blood of anemics has a somewhat higher inorganic salt content than that found in normal conditions.

SUMMARY

1. The results of the chemical and physical analysis of the blood in eighty-seven cases of pernicious anemia are reported.

2. The nonprotein nitrogen, urea and creatinin values are somewhat higher than normal. This is probably due, not to a permanent kidney lesion, but rather to the decreased amount of circulating blood.

3. The uric acid is much above normal.

4. The amino-acid content is greatly increased due to excessive destruction of serum protein.

5. The blood sugar is abnormally high.

6. The alkaline reserve is subnormal.

7. The last three point to the fact that in pernicious anemia the power of oxidation within the cell has been reduced to an abnormally low level.

8. The refraction and specific gravity are both astonishingly low, indicating deficiency in serum albumin, serum globulin and fibrinogen.

9. In most instances the freezing point is very near to normal. It is slightly raised in a small percentage of cases. This is due to the small increase of nonprotein nitrogenous substances and to the presence of normal or slightly increased amounts of inorganic salts.

XANTHOCHROMIA, WITH REPORT OF THREE CASES

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The association between xanthochromia and certain obstructive types of spinal cord tumors in the lower dorsal or lumbar regions is now well established. This association, however, is not so definitely determined that the discovery of xanthochromia justifies the diagnosis of a spinal cord tumor. There have been repeated instances of yellow fluid in the absence of tumor and it is in this type of patient that the significance of xanthochromia is not well established.

The character of the fluid in other respects, that is the coagulability, the amount of globulin, the number and type of cellular elements, permits of further classification of yellow fluids. Indeed, what is most characteristic and diagnostic about yellow fluids is afforded by certain features other than the color.

Reports of recent years make it evident that xanthochromia is not the uncommon finding that it is ordinarily supposed to be. Several large series of case reports from particular clinics bear this out. Nammack's series of ninety-six cases is, perhaps, the largest group reported. This series occurred in the examination of 5,801 spinal fluids by the meningitis division of the Health Department of New York City. This series was made mainly from acute or subacute types of disease. Sixty cases are tabulated and studied, and of this number fifty-three were instances of either tuberculosis, meningitis or poliomyelitis. Nammack's series differs, however, from Froin's syndrome in that coagulation was absent in practically all cases. Coagulation is recorded as three plus in one instance, two plus in one instance, and one plus in two instances and absent in the remaining cases.

The causation of the yellow fluid is not clear and apparently is not the same in all types of disease or pathologic states. The yellowish tinge of the spinal fluid which persists sometimes for long periods after the intraspinal administration of serum should not be considered as a true instance of xanthochromia. The albumin content may be increased in this condition also and persist for weeks after the serum has been administered. Froin believed that the yellow color was due to bilirubin and other blood pigment. It has been suggested that there are minute hemorrhages into the spinal canal and ventricular spaces to account for the yellow coloration. This type of hemorrhage does undoubtedly occur and there are instances where both red blood cells are found microscopically, and hemoglobin chemically.

The explanation of the absent hemoglobin reactions in certain instances of xanthochromia is not altogether clear. The reason has been advanced that decomposition or disintegration of the hemoglobin has taken place in the fluid which originally contained blood cells following minute hemorrhage. There is an occasional instance reported where the spinal fluid is discolored in icteric states, as in the case cited below. This type of discoloration should be excluded from the classification implied in the name xanthochromia. It is entirely probable that icteric spinal fluid would be found more commonly if spinal punctures were made in patients with jaundice. This occasion, however, rarely arises, for obvious reasons.

The list of pathologic states in which xanthochromia has been reported is fairly long and varied. A partial tabulation of this list is made by Sprunt and Walker in their excellent article. Xanthochromia has been found in such conditions as neoplasms of the cord or its membranes, vertebral tumors, vertebral fractures, tuberculous spondylitis, adhesions between the cord, arachnoid and dura, gumma of the meninges, gliosis spinalis with syringomyelia, myelitis, brain tumors in contact with the meninges or ependyma of the ventricles, tuberculous meningitis, poliomyelitis, Landry's paralysis, pachymeningitis, cerebral hemorrhage, epidemic meningitis, multiple sclerosis, verrucose veins of the cord, and neuritis of the cauda equina. This list is so varied that it is manifest that no etiology is common to all cases.

A division of cases of xanthochromia into groups on the basis of coagulability of the fluid will also throw them into groups in regard to pathogenesis. Increased coagulability of the spinal fluid is more pathognomonic than the xanthochromia itself. Instances of so-called massive coagulation of the spinal fluid practically always denote some obstructive lesion of the spinal canal. It is pointed out by Sprunt and Walker, that practically all authors agree that for the production of Froin's syndrome there is necessary an interruption to the flow of the cerebrospinal fluid and the formation of a pocket of greater or less extent in which the fluid stagnates and into which various elements pass by transudation from the blood vessels within its walls.

There are variations in the spinal fluid otherwise in regard to the cellular content, the amount and nature of the protein present, the presence of hemoglobin, which renders interpretation somewhat difficult. The fact that there are instances of yellow fluids which are still difficult or impossible to explain justifies the report of further cases.

REPORT OF CASES

CASE 1.—I. F., aged 20, male, student, was first seen Jan. 2, 1918.

Chief Complaint: Gradually increasing weakness of left leg during past six months.

Family History.—Measles and whooping cough in early childhood. Several attacks of sore throat. Denies venereal disease. Habits in regard to eating, tobacco, alcohol and sexual abuse negative. No history of trauma.

Present Illness.—The onset of the present illness is indefinite, but apparently dates from about June, 1917, since when he has had pains and increasing weakness in the left foot, leg and hip. The pains were trivial in nature at the outset, but increased in severity. Sometimes they radiated from the hip to the foot, again they affected more limited areas, such as the ankle, knee, calf or thigh. There was noted a distinct tendency to perspire freely, especially after exertion, however slight. Marked exertion was followed by actually dripping perspiration. During this first period there was no cough, dyspnea, expectoration, nausea, vomiting, headache, vertigo or disturbances of sleep. Later efforts at moderate work or even walking brought on palpitation. By the latter part of 1917, the movements of the left leg were markedly impaired, and eventually the foot dragged on walking. He was not able to stand without holding to some object. The pains in the legs had not increased over the earlier period, and were not intolerable. Sensory phenomena had appeared, such as numbness, tingling, and similar paresthesias. The tendency to perspiration continued and increased. Bladder incontinence developed and increased toward the end. Control of the rectal sphincter was fairly good, but not complete.

Physical Examination.—Temperature and respiration normal. Pulse rate variable, but reaching 120 on attempted effort or emotional excitation. Weight, 120; height, 5 feet 5 inches. Small frame, general musculature moderately developed, panniculus decreased. Bones, joints and glands negative. Patient lying in bed with hips and knees flexed. Is able to stand erect with some effort when aided or holding to some fixed object. Walks with great difficulty, dragging left foot and leg. Moderately fine tremor of hands increasing with excitement or effort. Expression anxious. Mental condition clear. Speech negative. Skin moist, no skin lesions or scars. No edema. Head negative. Teeth good, throat negative. No exophthalmos or other evidence of exophthalmic goiter. Thyroid palpable, but not enlarged, and without any bruit. Thorax slender, symmetrical, normal respiratory excursions, lungs negative. Heart not increased in size. Distinct cardiorespiratory murmur at apex and at the tip of the left scapula behind. Pulse rate, from 76 to 120. Synchronous on the two sides. No unusual vascular phenomena. Blood pressure, 122/60. Abdomen negative to inspection. Liver, spleen and kidneys not palpable. Genito-urinary system, negative.

Leukocyte count, 9,200. Hemoglobin, 90 per cent. Differential count: polymorphonuclears, 64 per cent.; small lymphocytes, 22 per cent.; large mononuclears, 9 per cent.; transitional cells, 4 per cent.; polymorphonuclear eosinophils, 1 per cent. The stained smear showed no unusual red cell forms, no parasites or other abnormal finding.

Examination of the nervous system showed no involvement of the cranial nerves or of the upper extremities. The two halves of the face were symmetrical. No twitching. Movements of the lids and eyes were normal in all directions. Pupils react well to light and accommodation. Movements of the mouth, such as whistling and blowing, were normal. Palatal reflex present.

Tongue protruded in median line without tremor. No atrophy of thoracic or muscles of upper extremity. All movements of hands and arms good. Moderate tremor of hands increasing on excitement or exertion. Spinal vertebra not sensitive to ordinary tapping with percussion hammer. Below the level of the sixth dorsal there are sensory changes which have no sharp line of demarcation. There are areas of complete anesthesia fixed from day to day, and also areas of disturbance of the temperature sense, but apparently varying from time to time. This condition of sensory changes extended from the trunk down the left thigh and leg to the ankle. The left leg showed a considerable degree of atrophy from thigh to the ankle. Both patellar reflexes were markedly exaggerated. Cremasteric and abdominal reflexes were absent on both sides. Babinski was marked on the left side, but absent on the right.

Spinal Fluid Examination.—Deep, rich canary color, not cloudy, cell count showed 22 cells per c.mm.; 18 of these were small lymphocytes; the remaining four cells were two or three times as large as a lymphocyte with a poorly staining protoplasm and nucleus. There was an excessively large amount of globulin, with partial spontaneous clotting after the second day. Wassermann reaction negative. Fehling's not reduced.

Operation.—Jan. 4, 1918, by Dr. J. H. Jacobson. Laminectomy was done and showed at the level of the fifth and sixth dorsal vertebrae a swollen, dark purplish, intramedullary growth gradually disappearing above and below this area. There was a very distinct difference in color of the cord above and below the tumor site. The meninges over this area were markedly congested, but not adherent to the cord by adhesions. The swelling of the cord blocked the vertebral canal completely. The fluid escaping below the tumor site was the same in all its characteristics as that removed at puncture but with the admixture of red blood cells. The fluid above the site of tumor did not appear to be stained yellow, but it was not possible to collect any portion of this for examination. The patient died eight hours after operation and a necropsy was refused. The tumor was inoperable.

The following case is an example of xanthochromia without the spontaneous coagulation which was present in Case 1.

CASE 2.—J. A. M., male, aged 27, locomotive fireman, married, first seen Nov. 2, 1916.

Chief Complaint: Patient came for examination complaining of headache and dizziness.

Family History.—Negative.

Previous History.—No disease of childhood. Had a gonorrheal infection at 17 lasting about one month. Denies any specific initial lesion or any skin rash. Two years ago there was again an urethral discharge lasting two weeks. Shortly after this there was a period when he had nausea and vomiting for several weeks. He was observed by several physicians and was told that he had syphilis, but does not know on what evidence this diagnosis was made. He was given at this time six intravenous injections of arsphenamin at intervals of two weeks. Dosage not known.

Habits in regard to alcohol, tobacco and eating not unusual. Patient has been married four years and has no children.

Present Illness.—Began in October, 1916, with convulsive seizures with marked jerking of the body while he was lying in bed. These convulsive move-

ments continued from early morning until toward noon of one day and during this period the efforts of the family to arouse him or get him to speak were unavailing. Later, he was confused and did not know what had transpired. Since this first attack there had been other similar ones coming on either during sleep or the day. Sometimes there would be slight convulsive movements which would initiate a prolonged period of unconsciousness, or there might be repeated convulsive seizures during a shorter period. Often the attack would begin with a jerking of the left hand, then a drawing up of the left arm. Several times the left half of the face was drawn up for periods of one or two hours after the convulsive attack. There was never any persisting facial paralysis. During the attacks there was incontinence of the bladder but not of the rectum. No speech disturbances persisted after the attacks. At first the patient persisted in his work between attacks, but was cautioned that such a course was very dangerous on account of the liability of the attack to appear while on duty, and stopped this work altogether.

Several months after the beginning of these attacks, the patient was found to have some sensory disturbances involving touch and temperature below the level of the seventh dorsal vertebrae. There were also sharp shooting pains down both legs and to the bladder region. Control of the bladder was not certain. During all this time the patient continued to complain of headaches and dizziness.

Physical Examination.—Examination showed temperature, pulse and respiration normal. Patient was tall, slender and rather under weight. There were no skin lesions or evidences of syphilis on the mucous membranes. There were moderately large palpable glands in the posterior region and also in both inguinal spaces. Epitrochlears not palpable. Between attacks the patient walked without ataxia, but had a rather peculiar slow hesitating walk. There was no tremor. The expression was anxious, as if he felt an attack pending at any time. The mental condition was clear and speech unimpaired. Throat, thyroid, lungs and heart did not show anything unusual. Blood pressure, 138/72. Arteries not hard. Radial pulses equal on two sides. The pupils were equal, reacted to light and in accommodation. Abdomen negative. Genito-urinary apparatus negative.

Examination of the nervous system showed no paralysis. There were definite sensory disturbances over the lower abdomen, posterior and lateral aspects of the trunk from the level of the seventh dorsal vertebra downward. The left thigh was involved in this disturbance also. There was definite anesthesia to pin pricks in several areas, but hyperesthesia was the rule, although this was not fixed from day to day. Thermal anesthesia was absent. Kinesthesia and astereognosis not present. The abdominal reflex was absent, also the cremasteric. The patellars were markedly exaggerated on both sides, Babinski negative on both sides.

At times following an attack, there was a slight weakening of the legs, but this was always transient. Kernig's sign negative.

Laboratory Examination.—The urine contained large numbers of shreds composed of pus cells and urethral epithelium. Gonococci could not be demonstrated in several stained specimens. Wassermann in the blood, four plus positive. Blood examination otherwise negative. Lumbar puncture showed a bright, canary yellow colored fluid not under pressure. There was a very large amount of globulin present, but no tendency to spontaneous coagulation. The lymphocytes were much increased in number varying from 78 to 140 per c.mm. The spinal fluid Wassermann was positive in all dilutions down to 0.1 c.c.

Treatment—Treatment was instituted with mercurial injections, potassium iodid, and arsphenamin in frequent injections of 0.3 gm. There were a number of attacks after starting treatment, but they ceased after the third month. The sensory phenomena on the trunk and thigh persisted for six to eight months in the main, although areas of hypesthesia and hypalgesia could be demonstrated as long as the patient was under observation. The xanthochromia remained at several punctures over a period of six months. A puncture made fourteen months after starting treatment showed a colorless fluid, but the globulin was large in amount; the lymphocyte count was 94 and the Wassermann was strongly positive. The patient consented to take intraspinal treatment, but received only one injection, when he refused further measures of this kind. Improvement continued so that he could resume ordinary labor and considered himself well.

The diagnosis in this case was taken to be a syphilitic pachymeningitis involving the brain and cord with gummatous involvement exerting pressure on the cord at the level of the lower dorsal region. The marked effect following treatment gives weight to this opinion. This type of syphilitic involvement of the meninges of the cord may take the type of a diffuse membranous exudation. There may be formations of new tissue (gummatous) involving not only the meninges but growing into the cord tissue. Gummatous formations are found sometimes on the nerve roots also. The symptoms are due to pressure.

Case 3 is an example of a yellow spinal fluid in jaundice. This is the type which Mestrezat calls xanthochromie d'origine icterique. Little attention has been paid to this type of yellow fluid because its origin is obvious and the absence of any special significance. Spinal puncture is not often done in cases with severe icterus because the structures concerned do not have to do with the nervous system. It is probable that the spinal fluid is stained in deep jaundice more than we believe.

Case 3.—E. C., aged 51, male, traveling man, American, came under observation July 18, 1919.

Chief Complaint: Repeated attacks of jaundice during the past twenty years.

Family History.—Negative.

Previous History.—Has always lived in northern latitudes, and has not traveled in the tropics. No history of malaria or dysentery. Had several attacks of tonsillitis in early childhood. Tonsils have not been removed. In 1899, had an attack of so-called muscular rheumatism which prevented him from carrying on his work for one month, but he was not laid up in bed. Recovered uneventfully and has had no recurrence. Diphtheria at 25. Denies venereal disease. Chews tobacco to excess, and smokes cigars moderately. Has been a very moderate user of alcohol.

Present Illness.—In 1904 jaundice developed without apparent cause and lasted six weeks. His physician did not make a definite diagnosis at that time. He carried on his regular work and did not feel particularly ill. The jaundice disappeared, but recurred in about two years under similar circumstances and

lasted three months. Again he was under the care of a physician, but no adequate explanation was given him for the jaundice. A third attack occurred about six years ago, and the last or present attack began in January, 1919. The jaundice has persisted since that time. At the outset of this attack and for several months following there were no symptoms of which the patient complained subjectively. He was conscious of the discoloration of the skin to a degree which made him rather morbid, but there were no special symptoms, such as digestive disorders, vomiting, or passing of blood. There was no cough. Later in the fall of 1919 there developed slight dyspnea on exertion. There was no change in weight. No disturbance of urination. No chills, sweats, headaches or vertigo. Toward the latter part of 1919 there developed rather marked symptoms on the part of the nervous system. There was marked paresthesia over the trunk and abdomen, crawling, prickling, tingling in nature. These sensory phenomena became so troublesome that sleep was disturbed and the patient became very despondent and melancholy. He shunned the street on account of the attention he attracted from his deeply jaundiced state. Later there were shooting pains down his legs and in his back. It was on account of these symptoms that a spinal puncture was done.

Physical Examination.—Patient is a medium sized man, weighing 151 (normal 175) pounds. Temperature, from normal to 99 degrees. Pulse 80, respiration 16. Patient has a very restless manner and appears to be nervous and irritable. No palpable glands, no lesions of the skin or mucous membranes. The skin of the entire body is stained a very dark, greenish yellow color. The sclerae are also deeply stained. There is no pigmentation of the buccal mucous membranes. Tonsils and teeth are good. Lungs are negative. Heart is normal in size. Soft, blowing systolic murmur brought out after effort test. Blood pressure, 140/70. The abdomen shows no enlarged veins. The liver is enlarged fully a hand's breadth below the ribs. The margin is rather blunted, the surface is smooth and not tender. The spleen is moderately enlarged and slightly tender. No fluid in the abdominal cavity. No edema of the legs.

Laboratory Examination.—Urine: sp. gr., 1.022, deeply stained with bile which is present in large amounts; albumin present in large amounts; no sugar; many deeply stained yellowish hyalin and granular casts; no blood or pus. Gastric analysis negative. Stools dark in color; no parasites or blood. Blood Wassermann negative. Spinal puncture showed a fluid under moderately increased tension, color dull brownish yellow (not the clear canary color found in the cases just cited), globulin present in increased amount, but not excessive, no spontaneous coagulation, cell count 18 per c.mm. all small lymphocytes, Fehling's not reduced, blood tests negative. Wassermann negative in all amounts up to 2.0 c.c.

Diagnosis.—Biliary cirrhosis of unknown etiology.

It is apparent that all types of xanthochromia indicate an organic disease but not necessarily of the nervous system. The presence of the yellow color is not in itself pathogenic, but the Froin syndrome is practically so. It is apparent that clinical signs otherwise are apt to be very definitely outlined by the time that a disease process has advanced far enough to produce an obstructive lesion within the spinal canal and the isolation of the lumbar culdesac, but whatever its nature, the Froin syndrome if present is confirmatory to the greatest

degree. It is doubtful if the Froin syndrome ever occurs in condi-
tions other than obstructive lesions of the spinal canal. The very
few instances in which this syndrome has been reported in acute con-
ditions such as tuberculous meningitis or poliomyelitis, can be
accounted for on the assumption of an interference with the con-
tinuity of the spinal canal from an exudative process or an extravasa-
tion of blood.

CONCLUSIONS

1. There are many conditions which may cause a yellow spinal
fluid.

2. The great variability in the disease processes in which xantho-
chromia has been found renders the color itself of no diagnostic
value.

3. A yellow fluid is always diagnostic of an organic lesion or infec-
tious process with the exception of those cases in which serum has
been injected intraspinously.

4. The presence of the Froin syndrome is pathognomonic of an
obstructive type of spinal lesion.

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A STUDY OF THE CORRELATION OF THE BASAL METABOLISM AND PULSE RATE IN PATIENTS WITH HYPERTHYROIDISM *

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. Since the first description of the syndrome known as hyperthyroidism, tachycardia has been noted as one of its classical signs, and until more recent years a careful study of the pulse rate was regarded as probably the most valuable single objective test from the standpoint of diagnosis, and as an indication of the severity and course of the disease. More recently it has been held that the determination of the basal metabolism gives a more accurate estimate of the degree of hyperthyroidism than has hitherto been possible. An intensive study of the basal metabolism in hyperthyroidism is being carried on at the Peter Bent Brigham Hospital, and it seemed worth while as an incident in this to attempt to correlate the changes in pulse rate with basal metabolism. If a fairly definite and constant relationship exists between the two, one then would have the means of roughly estimating the height of the basal metabolism. This would be of value as the actual determination of the basal metabolism is somewhat complicated and not available to many patients with hyperthyroidism. DuBois has also suggested that a study of a large series of patients with exophthalmic goiter to ascertain the relationship between the elevated metabolism and the more prominent symptoms and signs of the disease would be of importance.

It is known that certain symptoms and signs of hyperthyroidism, such as tachycardia, loss of weight, warmth of skin and sweating, are directly referable to the increased heat production, either entirely or in part, and hence they are indirectly a measure of the presence or absence of increased metabolism, and roughly the degree of increase. With an increase in metabolism there is a greater demand for oxygen by the body cells. This demand is met by increasing the amount of air breathed per minute and by circulatory changes which augment the blood flow. The increase in heart rate may be regarded as one of the compensatory factors which permits a larger amount of oxygen to be delivered to the body cells. Hence, theoretically, it would be expected that an increase in metabolism would be constantly associated with a tachycardia, provided certain complicating factors, as for instance, heart block, were not present. Of the signs directly referable

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to the increased heat production, the most simply and easily determined is the pulse rate and, therefore, a series of patients with hyperthyroidism and increased metabolism have been studied in order to ascertain the precise relation of the pulse rate to the increased heat production, and also to determine the value of the pulse rate as an indication of the presence or absence of hyperthyroidism and as a guide to the degree of over-activity of the thyroid gland.

LITERATURE

Benedict and Murchhauser [1] emphasized the fact that there is an apparent striking relationship between metabolism and pulse rate in normal subjects. They made observations before and after a light meal, during sleep and while awake, and after changing from the lying position to a sitting position, and noted that with the resultant percentage increase in metabolism there was a simultaneous and corresponding increase in the pulse rate, indicating a quantitative relationship. In their experience there was no such relationship in a comparison of different persons; hence, the relationship between pulse rate and metabolism holds only when the records are obtained from a single individual. DuBois [2] commented on the correlation between the heart rate and basal metabolism in patients with exophthalmic goiter, and thought the rapidity of the heart action to be the best guide of the simpler objective tests in determining the severity of the disease and its course. · He did not believe it to be an altogether accurate index of the patient's condition as the heart might be affected by other conditions than hyperthyroidism and damage to the heart might outlast other symptoms.

Means and Aub,[3] in a study of the basal metabolism in exophthalmic goiter, noted a close parallelism between the pulse rate and metabolism in about 60 per cent. of the cases, while in the remainder there was a certain amount of parallelism. They concluded, as Benedict and Murchhauser emphasized in normal subjects, that there is little relationship between the heart rate and metabolism in different individuals, but in a single individual the resting pulse rate is a tolerably good index of the patient's progress.

White and Aub [4] studied the electrocardiogram in forty-seven patients with exophthalmic goiter and concluded that there was only

1. Benedict, F. G., and Murchhauser, H.: Energy Transformations During Horizontal Walking, Carnegie Institution of Washington, Publication 231.

2. DuBois, E. F.: Metabolism in Exophthalmic Goiter, Arch. Int. Med. **17**: 915 (Dec.) 1916.

3. Means, J. H., and Aub, J. C.: The Basal Metabolism in Exophthalmic Goiter, Arch. Int. Med. **24**:645 (Nov.) 1919.

4. White, P. D., and Aub, J. C.: The Electrocardiogram in Thyroid Disease, Arch. Int. Med. **22**:766 (Dec.) 1918.

a moderate parallelism between the degree of tachycardia and the basal metabolism increase.

Peabody, Wearn and Tompkins [5] found the basal metabolism to be normal in soldiers with "irritable heart" and observed that while these patients often. have a marked tachycardia when under a mental or physical strain, it differed from the tachycardia of hyperthyroidism as it disappeared if the patient was permitted to lie down for a short period.

MATERIAL

The observations on the metabolism and pulse which form the basis of this report were made at the Peter Bent Brigham Hospital between the years of 1914 and 1920. In the ninety-nine patients with hyperthyroidism who have been studied, the metabolism was elevated when they were first observed. In a majority the metabolism has later become lower as a result of thyroidectomy, ligation of the thyroid arteries, or a combination of the two, or as a result of rest and in a few instances following exposure to the roentgen rays. In these patients, then, the relationship between the pulse rate and metabolism has been studied at intervals during the course of the disease. To form a comparison with our own results a series of metabolism studies and pulse rates have been analyzed from the report of Means and Aub.

METHOD

The method used in all metabolism determinations were standard ones and need be described only briefly. After the patient had been fasting for from twelve to fourteen hours, and at a time when the resting pulse had reached its lowest level, a facemask was applied and the expired air was collected in a 100 liter modified Tissot spirometer. Analysis of the expired air was then done with a portable Haldane gas analysis apparatus. The heat production in calories per square meter per hour was then computed and compared with the normal standards of DuBois, and the result expressed in percentage of normal. During the metabolism determinations the pulse was counted six to nine times, and the average of these counts have been taken as the pulse rate in this report. While +10 per cent. has been given as the upper limit of normal of metabolism, a great deal of importance cannot be attached to slight increases over this and hence in this study the upper limit has been placed at +15 per cent.

In order to be of value the pulse rate in patients with hyperthyroidism must be taken with considerable care. The pulse should be

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5. Peabody, F. W.; Wearn, J. T., and Tompkins, E. H.: The Basal Metabolism in Case of "Irritable Heart" of Soldiers, M. Clinics N. America **2**:507 (Sept.) 1918.

determined when the patient is lying flat in bed and when there is
mental quiet. The rate should be counted at five-minute intervals for
half an hour or until the pulse has reached a level. Probably the
most desirable procedure is to count the pulse while the patient is
asleep, as this has the advantage of greatly reducing psychic stimuli,
which are one great source of error. Recently this has been carried
out with considerable success at the Peter Bent Brigham Hospital, but
it is not possible in all cases.
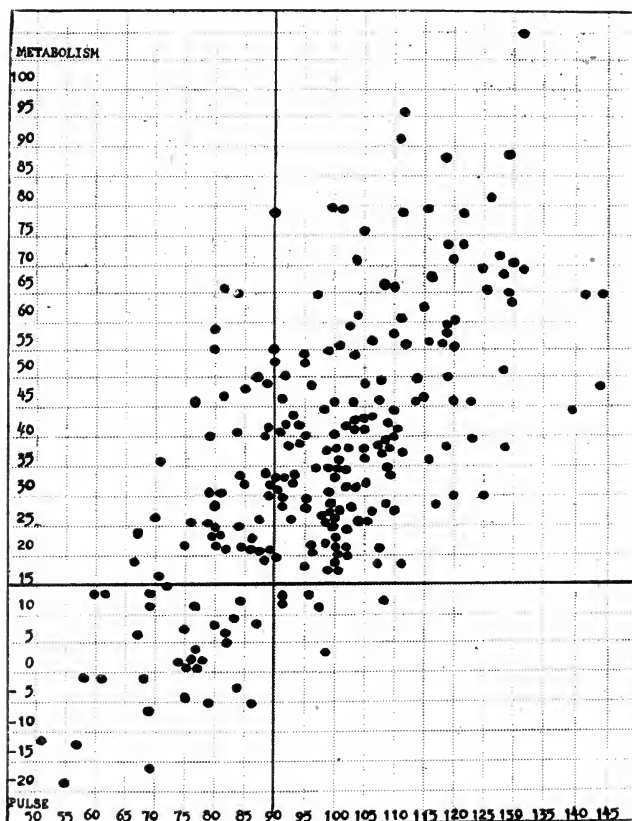
Fig. 1.—Two hundred and thirty-eight observations charted according to
pulse rate and basal metabolism. All of the dots in the upper right square
indicate the observations with a metabolism greater than + 15 per cent. and
pulse 90 per minute or greater; in the left upper square are those with metab-
olism greater than + 15 per cent. but pulse below 90; in the right lower square
are those with a metabolism below 15 per cent. but pulse greater than 90,
and in the left lower square are those with a metabolism below + 15 per
cent. and pulse below 90. It is apparent that a composite curve of all the dots
would indicate the general tendency of the tachycardia to be more marked in
patients with a high metabolism and of a less degree in those with a low
metabolism.

THE PULSE RATE IN PATIENTS WITH A NORMAL
BASAL METABOLISM

In order to determine the frequency of a tachycardia while at rest, the pulse rate was studied in a series of 106 patients with a normal metabolism. Fifty-four of these patients were observed at the U. S. Army Hospital No. 9, by Peabody, Wearn and Tompkins, and in each instance the final diagnosis was "irritable heart," although in
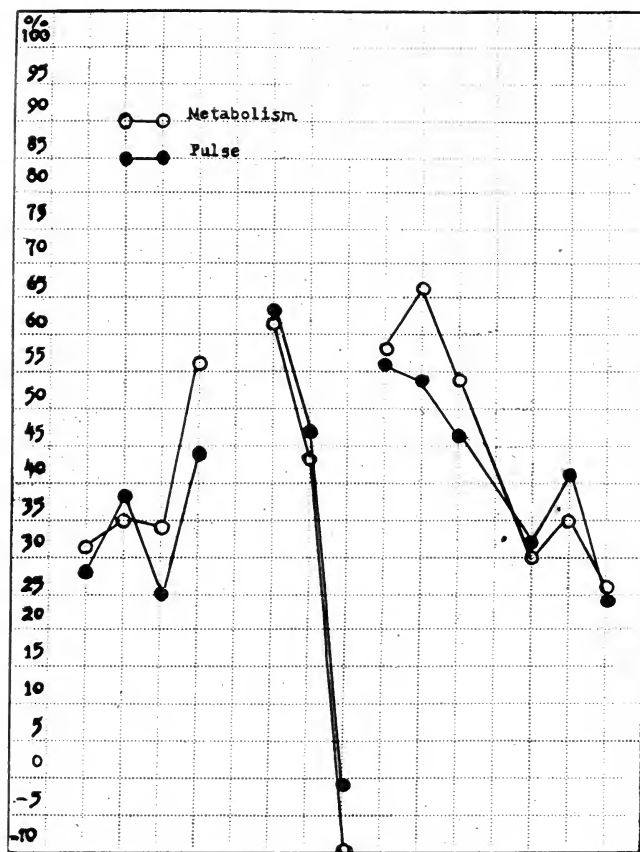
Figure 2

twenty-six cases the transfer diagnosis was hyperthyroidism. In only two cases was the pulse rate above 90 and in only eight was it above 80, although in such persons there is a tendency to a marked tachycardia, reaching 120 or 130 on slight mental or physical strain. As has been emphasized, the fall of the rapid heart action to normal when at complete rest is very helpful in indicating that the metabolism is not elevated, and that these patients did not have hyperthyroidism.

The remaining fifty-two hospital patients with normal basal metabolism had various diagnoses, but those conditions were excluded which in themselves tend to give a tachycardia, as, for instance, organic heart disorders. In the total of 106 patients with a normal metabolism, only five had a pulse of 90 or over when at rest. In only one instance was the rate greater than 100. It is difficult to state just what the normal heart rate should be in a perfectly healthy person. It has
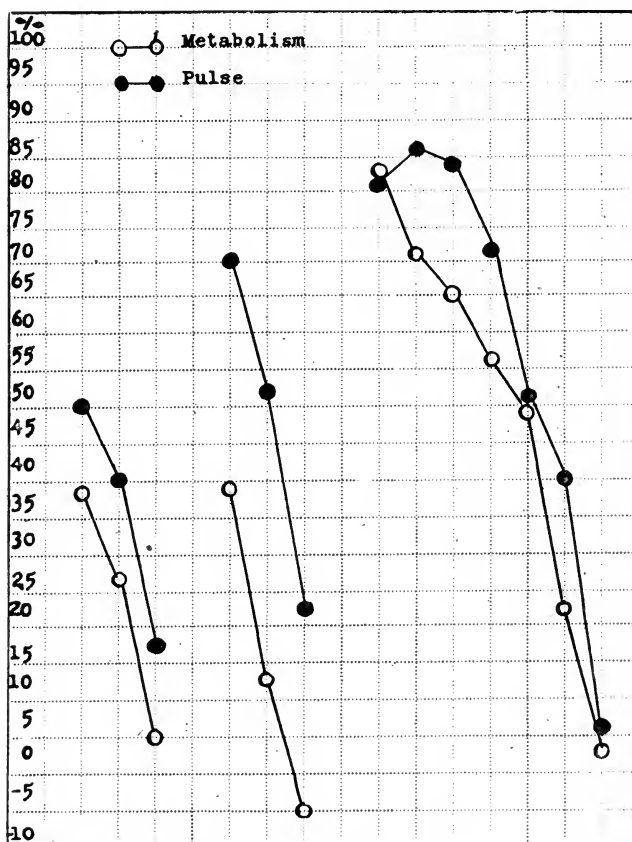
Figure 3

been found that athletes in Oxford had rates which may be considered normal that range between 44 and 80 per minute. In a study of medical students at Cambridge the range was between 47 and 90.[6] It seems safe to say, however, that, provided other conditions are ruled out which in themselves cause a tachycardia, persons with a

6. Air Service Medical, War Dept., Air Service, Washington, D. C., 1919, p. 147.

normal metabolism rarely have a resting pulse rate as rapid as 90 to the minute, and in a majority the rate is below 80.

PRESENTATION OF DATA

A total of 496 basal metabolism determinations on ninety-nine patients with hyperthyroidism from the Peter Bent Brigham Hospital
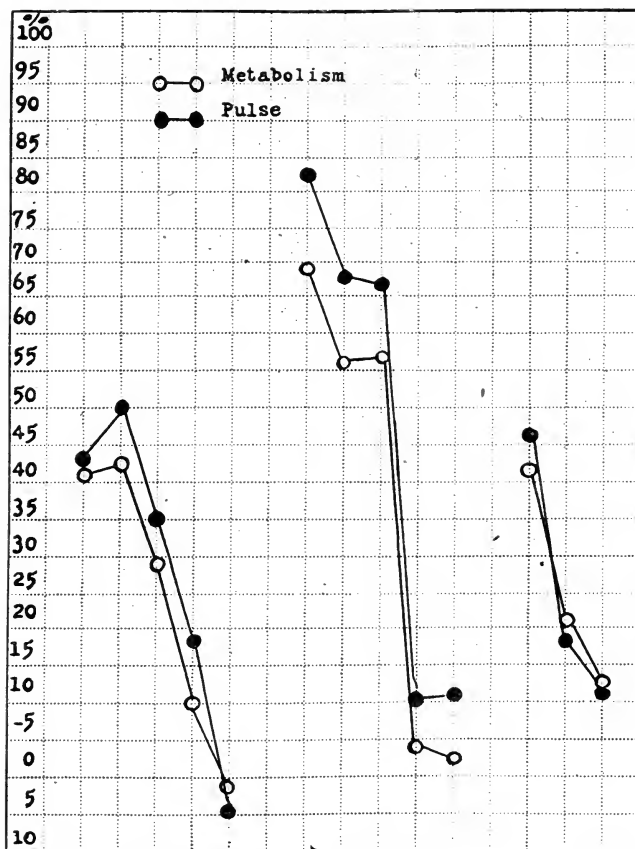
Figure 4

Figures 2, 3 and 4 illustrate the parallelism between the basal metabolism and pulse rate as shown by a series of observations on nine patients with exophthalmic goiter. The pulse and metabolism have both been charted in per cent. of normal, the normal pulse having been considered 70 per minute.

and fifty-five patients as reported in the paper by Means and Aub, have been studied. In 426 instances there was a basal metabolism of +15 per cent. or greater, while in seventy the metabolism was below +15 per cent.. The latter group was made up of patients included in

the former group where metabolism studies had previously shown an increase, but subsequently there had been a decrease to below $+15$ per cent.

Of the 426 determinations with a basal metabolism elevated above $+15$ per cent., the resting pulse rate was 90 per minute or more in 84 per cent., 85 or more in 91 per cent., and 80 or more in 95 per cent. Or in other words, there was a tachycardia of 90 or greater associated with the increased metabolism in all except 16 per cent., and in all but 5 per cent. the pulse was above 80. Judging from these figures, then, it seems fair to conclude that in a majority of patients with hyperthyroidism, or in those in whom the diagnosis is in doubt, a persistent heart rate of 90 or over when the patient is at rest indicates an increased metabolism, provided other obvious causes for the tachycardia can be eliminated.

Of the seventy instances where the metabolism had been elevated but later fell below $+15$ per cent. there was a simultaneous fall in the pulse rate below 90 in 78 per cent. Hence, a resting pulse below 90 per minute indicates in a large percentage of patients with hyperthyroidism that the metabolism is not increased, and as the heart rate shows a greater decrease it suggests this still more definitely. The fact that one rarely observes an increased metabolism with a normal or slow pulse is of considerable practical importance and the value of this relationship is not appreciated by many. A resting pulse below 90 per minute, usually means that the metabolism is normal, and a slower pulse, as, for instance, 70 per minute, almost certainly indicates a normal metabolism. This fact is of practical importance in the recognition of the large group of nervous patients who have signs and symptoms similar to those in hyperthyroidism. In some cases the metabolism falls to normal, but the pulse rate does not drop to below 90 per minute, and it is possible that this is due to the fact that the heart has become seriously affected.

Probably the most accurate interrelation between the pulse rate and the amount of heat production is to be found during the course of the disease in any one patient. In a series of fifty-two patients with hyperthyroidism, on whom two or more metabolism observations had been made, changes in the pulse gave an accurate idea of those in the heat production in the subsequent observations in 85 per cent. of the cases. The heart rate remained at a constant level if the metabolism was unchanged and indicated fairly accurately the degree of rise or fall in metabolism if such occurred. Hence, in following the course of the disease in a patient with hyperthyroidism the resting pulse rate compares very favorably with the basal metabolism as an index of the patient's condition.

The series of 238 metabolism observations from this hospital were arranged according to the degree of tachycardia to see if in a group of patients there was a relationship between the level of heat production and the rapidity of the heart. It is hardly to be expected that a given heart rate would always correspond to the same elevation of metabolism in different persons, because of the variations of the normal pulse rate in different individuals. In spite of this, however, there is a suggestive or partial interrelation between the increase of the pulse rate and metabolism, not only in a given person, but also in a group. Thus, where a considerable number of observations are considered one finds that the average pulse rate bears a fairly definite relationship to the metabolism. For instance, in all observations with a pulse rate between 90 and 99, the average basal metabolism of the group was +36 per cent., while in those with a rate between 100 and 109 the average was +41 per cent., and in those with a rate between 110 and 119 the metabolism was +59 per cent. There are, however, many individual discrepancies. These occur particularly in a group of cases in which the metabolism is greatly elevated, and the pulse rate relatively slow. Nevertheless, one may usually expect a marked tachycardia associated with a high metabolism and conversely a relatively slow pulse with a metabolism that is normal or moderately elevated.

STUDY OF PATIENTS WITH A RELATIVELY SLOW PULSE AND ELEVATED BASAL METABOLISM

A careful study has been made in an endeavor to discover a cause for the occasional low pulse associated with the increased heat production, and to classify these causes into groups. In a majority of cases this has not been possible. Patients with auricular fibrillation and heart block, however, can account for a discrepancy in a certain number of instances. Auricular fibrillation is not an uncommon form of arrhythmia in hyperthyroidism, while either complete or partial heart block is met with infrequently. Of the series of forty-three determinations with an increased metabolism and a pulse below 90 to the minute there were seven determinations on four patients with auricular fibrillation, and one with partial heart block. The remaining patients of this group gave no clinical evidence of an arrhythmia, but in only two were electrocardiograms taken.

In three patients the slow pulse with an elevated metabolism may possibly be explained by the fact that normally the individuals had an unusually slow pulse. In these three individuals when the metabolism returned to normal the pulse rate fell in one instance to 57, in another to 52, and in a third to 55. Had it been possible to observe

the other patients of this group when their metabolism became normal, likewise their pulse rate at this time might have been abnormally low.

There then remains a majority of this group where there is no discoverable cause of the discrepancy between pulse rate and metabolism.

SUMMARY

A study of the resting pulse rate and basal metabolism in hyperthyroidism shows that there is a fairly constant relationship between the two in a high percentage of instances. In a study of 496 basal metabolism determinations on 154 patients with hyperthyroidism, there was a tachycardia of 90 or more to the minute, associated with a basal metabolism of $+15$ per cent. or more in all but 16 per cent. In seventy instances when the metabolism fell to normal there was a simultaneous fall in pulse rate in 78 per cent. to below 90. In fifty-two patients on whom a number of metabolism determinations were made, the pulse rate gave an accurate idea of the course of the disease as compared to the basal metabolism in 85 per cent. In a series of 106 hospital patients with various diagnoses and normal basal metabolism only five had a heart rate of 90 or more to the minute. There is in general an interrelationship between the pulse rate and metabolism when a group of individuals are considered; that is, an extreme degree of tachycardia suggests a greatly increased metabolism while a slight tachycardia usually indicates a slight or moderate increase. The fact that a pulse rate at complete rest below 90 per minute is seldom and below 80 per minute is rarely associated with an increase in metabolism is of practical importance in the recognition of the large group of nervous patients who have symptoms similar to those occurring in hyperthyroidism.

NEURITIS OF THE CRANIAL NERVES IN LETHARGIC ENCEPHALITIS AND THE DIFFERENTIAL ANATOMIC DIAGNOSIS BETWEEN IT AND ACUTE POLIOMYELITIS *

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In looking over the literature of the histology of lethargic enceph-alitis which has accumulated during the last few years, it was of interest to .note that no one has made mention of the inflammatory changes which may occur in the cranial nerves in these cases. Since this fact may be of importance in clearing up and explaining many of the clinical symptoms, in subsequently giving aid for the solution of the etiology of this affection and in differentiating it pathologically from acute poliomyelitis, it became of interest to study more care-fully the material obtained from the necropsies made in three cases and to report ·the findings with abstracts of the clinical histories. These cases were treated and died in the Barnes Hospital, and the abstracts of the clinical histories reported in this paper are taken from the histories which are filed there.

REPORT OF CASES

CASE ·1.—J. H. T., male, negro, aged 46 years, chauffeur, was admitted to the hospital, Feb. 14, 1919, in the service of Dr. George Dock. The patient complained of a general run down condition and failing eyesight. The family history was not important.

Past History.—His past history has also been uneventful. He does, not remember ever having been sick before the present illness. He denies syphilis and gonorrhea and gives no history which would indicate his having had the same. He has followed the profession of chauffeur for the last twelve years. He has never married. He eats regularly and drinks two or three glasses of whisky, 2 or 3 pints of beer and 1 cup of coffee a day but he takes no tea or drugs.

Present Illness.—This commenced three weeks ago. The first symptom was weakness of vision. This bothered him in driving a car. A physician was consulted who told him he was losing his eyesight and gave him an eyewash. He has had no headache and he has not had complete loss of vision at any time.

His appetite is good. He has had no fever, chills, pain of any kind, nausea or vomiting, but during the whole of the last month his bowels have moved but once a week. There has been no loss of weight, no cough, no urinary symptoms. Aside from the changes in vision his only complaint is weakness. He feels tired all the time and wants to lie down and when he does he always falls asleep. During the last week he has slept excessively.

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* From the pathological laboratory of the Washington University School of Medicine.

There has been no loss in motor power, no yawning. His memory is good, and he has had no ringing in his ears, no dysphagia, no vomiting, no subjective sensation. It has been noticed recently, however, that he hesitates before answering questions and he says he has double vision.

A physician who knows him states that he recently developed a corneal scar in the left eye. This was noticed first by him about February 3 or 4. This physician also says that during the last month he has had four automobile accidents and all were on the left side. They were ascribed to defective vision of the left eye caused by the scar. He also complained ten days ago to this physician of pain in his left leg. His leukocyte count at that time was 5,700. There was no abdominal rigidity and no deep tenderness. The pain moved later to the right sacro-iliac region, and disappeared entirely when the patient was put to bed.

Always in the past the patient answered questions quickly and promptly. The first indication of altered speech began February 9. It was also noticed at that time that he tilted his head forward and to the left. He has been in bed most of the time recently. No abnormalities of gait have been noticed.

Physical Examination on Admission.—The patient is lying quietly in bed. He seems oriented, but answers questions slowly. He knows his name, age, day of the week but not the date of the month. He says Christmas was two months ago but stutters when he says it. His speech is thick and he stares straight ahead but does not complain of pain. In fact, he says he feels fine. His eyes do not move when he speaks. The eyelids move occasionally. His head is also held fixed. The skin of the face is greasy. He says he has put nothing on it. The skin in other parts of the body is smooth, moist and elastic but slightly hyperesthetic. The panniculus is thick. The muscles are large and firm.

Head: The face is expressionless. The lips are open 2 mm. Part of the hair is gray. The eyes move well to the right but poorly to the left. One mm. of sclera always shows on the left side. Upward movements are limited to 2 mm. He cannot move his eyes downward. Both upward oblique movements are present to a slight extent. Downward oblique movements are made readily. Both eyes move synchronously. There is slight nystagmus in the vertical direction and slight internal strabismus of the left eye but no convergence.

Nose: It is red and dry. The septum is deviated to the right and there is a polyp in the posterior nares on the right side.

Mouth: The tongue protrudes in the midline and has a median coarse tremor. It is pointed, gray and coated. There is a marked pyorrhea alveolaris. There is a slight reflex response to touching the pharyngeal wall. The tonsils are on a level with the fauces and reddened. The voice is hoarse. The larynx is not examined.

Ears: The right drum looks red. The left is retracted. There is no discharge.

Neck: There are no palpable nodes. The thyroid is not enlarged. The jugular pulsation is marked.

Chest: It is large. The clavicles are prominent. The respiratory movements are shallow. They are 22 per minute, and costo-abdominal in type. They lag slightly on the left. The percussion note is resonant, except at the left apex. The breath sounds are weak throughout but louder at the left apex. There are no râles heard in front. The spoken voice sounds are well transmitted. Behind the breath sounds are heard only at the left apex and there are showers of very fine crepitant râles heard over the right lower lobe.

Heart: The cardiac dulness is 12 cm. to the left and 3 cm. to the right of the midsternal line. There are no murmurs. The aortic second sound has a slightly ringing quality. The walls of the radial arteries are thickened. The pulse is 100 per minute. The blood pressure is 154/112 on the right side and 150/112 on the left.

Abdomen: The liver, spleen and kidneys cannot be felt. The level of the abdomen is below the costal margin. It is soft throughout and there are no areas of tenderness. The epigastric and lower abdominal reflexes are absent. The midabdominal reflexes are occasionally present on both sides.

Upper Extremities: The reflexes on the right side are slightly more active than on the left side. The periosteal, biceps and triceps reflexes are elicited on both sides. The digital reflexes are absent. The epitrochlear glands are not palpable. The skin of the hands is dry. There is no limitation of motion. The fingers are held in a claw-like position. This changes during examination. Resistance is given to any passive movements of the arms or hands.

Lower Extremities: The knee kicks are equal and active. The response varies at times. There is no patellar or ankle clonus, Oppenheim, Gordon or Chaddock's sign. The skin of the feet is dry. The cremasteric reflexes are equal and active. The right responds more quickly than the left. The skin over the edge of the right tibia is roughened.

During the examination the patient holds his neck rigidly, and when told to raise his body he cannot do it. With help he raises his trunk but always holds his neck in the same rigid position. His movements are slow. He gets out of bed slowly and carefully without at any time moving his head sideways.

Gait: He walks slowly. His body tends to fall to the right and his head is held over to the right side. His gait is slightly spastic and there is no wide base. His steps are short and shuffling and there are indications of definite weakness. Romberg's sign is negative. Heel to knee and midthigh movements are good. There are no Kernig or Babinski signs.

Genito-Urinary System: The testicles are negative, and there are no penile scars.

Rectum: The sphincter tone is good. The prostate is enlarged, roughened and slightly tender. There are no definite nodules.

Eye Grounds: Both lids are red. Their edges are distinct. There is no choking of the disks. The lamina cribrosa markings are perfectly clear. There are no hemorrhages or tubercles. The media are clear. The vessels of both eyes are tortuous, but this is more marked in the right eye than in the left.

Clinical Course.—February 17, three days after admission, the right eye shows upward deviation. The left rotates inward. A lumbar puncture is made. Arsphenamin, 0.3 gm., is given, but there is no immediate reaction.

February 19: The patient is more drowsy. The rigidity is as before. The pulse is rapid.

February 21: Kernig is marked. The respirations are shallow, 38 per minute. The pulse is 140. The diagnosis of encephalitis lethargica is suggested.

February 23: A stereoscopic roentgenogram of the skull is reported negative. The patient dies at 5:45 p. m.

The pulse during his stay in the hospital ranged between 100 and 150. The temperature on admission was normal. It rose gradually to 102 F. and it was 103 F. just before death.

Laboratory Findings.—Urine: No albumin, sugar or casts were ever found. A few red blood cells were seen once.

Blood: February 17, the blood nitrogen measured 62.35. February 15, there were 7,000 leukocytes. February 22, there were 10,700 leukocytes, the differential count showing 76 per cent. polymorphonuclear leukocytes.

Lumbar Punctures: The first was made February 17. A small amount of blood was seen in the first part. The remainder was clear. The Ross-Jones test was positive. Fehling's test was negative. The cell count was 39 lymphocytes, 1 polymorphonuclear leukocyte and possibly 1 red cell per c.mm.

The second lumbar puncture was made February 23. The fluid was clear and contained 52 lymphocytes, 2 polymorphonuclear leukocytes per c.mm.

Fehling's test was positive. Smears were made from centrifuged specimen and stained for tubercle bacilli. These were negative and inoculation of the same material to guinea-pigs gave no result.

The sputum was always negative.

The Wassermann tests on blood and spinal fluid were negative. Complement fixation for tubercle bacilli was negative. The colloidal gold reaction was in the luetic zone.

Clinical Diagnosis. — Arteriosclerosis, general; meningitis (?); lethargic encephalitis (?).

The necropsy was performed two days after death by Dr. Hans P. Andersen. The brain was studied by him and myself. The body was kept in the morgue at a temperature of 4 C. during the period between the time of death and the necropsy.

Necropsy Report.—The body is that of a well nourished, muscular, male negro. It weighs 56.5 kilos and measures 172 cm. in length. The skin shows no marks or discolorations. The body cavities are smooth, moist and glistening. They contain no excess of fluid.

Heart: Weight, 400 gm. The valves measure as follows: Aortic, 9.5 cm.; mitral, 11 cm.; pulmonary, 7.5 cm.; tricuspid, 13 cm. The muscular portion of the wall of the left ventricle measures 15 mm.; the right, 4 mm. The myocardium shows no changes. There are many irregular yellow placques in the intima of the aorta, along the bases of the mitral and aortic valves and in the endocardium of a part of the left atrium. These placques are thicker and more fibrous about the orifices of the coronary arteries. The heart otherwise shows nothing of interest. Atheromatous changes are seen throughout the whole course of the aorta. The aorta has little elasticity and the atheromatous changes are most marked about the orifices of the branches and in its abdominal portion. The coronary arteries and many of the other branches of the aorta also show changes of a similar character.

Lungs: They are free in the pleural cavities. Their surfaces are smooth. Their upper lobes have a pink color while the more dependent portions are colored a deep purple mottled by numerous bluish red subpleural hemorrhages. On section the dependent portions have the same deep purple color while the anterior portions of the upper lobes are bright red. These portions of the upper lobes are air containing and they are tough and leathery while from all other portions a bloody, frothy fluid can be expressed.

Spleen: Weight, 60 gm. and measures 10.5 by 6 by 2 cm. The capsule has a slaty color. The organ is soft and flabby. On section, there is a marked increase in connective tissue. The malpighian corpuscles are not prominent and the pulp is increased.

Liver: Weight, 1,640 gm. and measures 32 by 17.5 by 6 cm. It is long in the transverse diameter but thin anterioposteriorly. The capsule is smooth, thin and translucent and it transmits a dark brown color. On section, the lobules are easily made out They appear slightly enlarged. Their centers are deep red in color. Their peripheries have a grayish yellow appearance.

Pancreas: It shows nothing unusual, except that the walls of the splenic artery and the pancreatic arteries are irregularly thickened.

Stomach: The mucosa is congested and in places, hypertrophic and mammillated.

Intestines: Show nothing of interest except the duodenum and upper part of the jejunum. Here the mucosa appears swollen and it is deeply congested. The mesentery contains a moderate amount of fat. The mesenteric lymph glands are not enlarged. The retroperitoneal lymph glands are also not enlarged.

Suprarenals: Appear normal.

Kidneys: Weigh together 360 gm. They are equal in size, each measuring 11.5 by 6 by 3 cm. The cortices each measure 6 mm. The capsules are slightly adherent in places to large, slightly sunken, scarred areas. On section, the

medullae are found to be congested. The glomeruli are also easily seen as small red pin point sized areas. The outer edges of the cortices of both kidneys are slightly rounded. The striations of the cortices are straight except in the scarred area. The gray columns appear thickened.

The ureters and bladder appear normal.

The prostate is enlarged, otherwise it shows nothing of interest. The enlarged middle lobe causes no urethral obstruction.

Brain and Spinal Cord: The dura is adherent to the cranial bones above. The meninges of both the cord and brain are deeply congested and there is edema of the meninges of the cerebral cortex. There are also several small, irregular, gray fibrous patches in the meninges of the cerebrum. The walls of all the larger blood vessels are thickened and rigid. They also contain numerous yellow and gray elevated placques which measure from one to several mm. across. Between these placques the vessel walls have a slightly grayish opacity.

The cut surfaces of the spinal cord and medulla are smooth. There is no bulging out of the medullary substance. It is congested but not tensely swollen.

The meninges covering the anterior surface of the pons and midbrain are slightly cloudy. This is not striking but it is readily brought out by contrasting them with a normal brain.

The brain and spinal cord are placed in liquor formaldehydi to be examined in greater detail after fixation.

Microscopic Examination.—Heart: The striations are not clearly defined. The fibers are granular and fragmented.

Lungs: Section 1. The atrial cavities are dilated. The blood vessels are congested. The alveoli and atria contain a small amount of pink staining granular material. Red cells are also seen in the alveoli along one side of the section together with a few large pigment laden mononuclear cells. The pigment in these cells has a brown color. The bronchial epithelium is in part desquamated.

Section 2. The blood vessels are congested. Many of the alveoli are filled with pink staining granular material. Others contain also many polymorphonuclear leukocytes and large mononuclear cells. The nuclei of the epithelial lining cells are prominent.

Spleen: The artery walls are thickened and hyaline. The trabeculae are thickened and fibrous. The malpighian corpuscles are numerous, small and cellular. In places they are sharply demarcated from the pulp spaces. In other places their boundaries are not so distinct. The endothelial nuclei of the pulp spaces are numerous and prominent. The pulp spaces contain · a few polymorphonuclear cells and many small mononuclear cells in excess.

Liver: The parenchymal cells are swollen and granular. The intima of the smaller hepatic arteries is irregularly thickened and fibrous. The liver capsule is slightly thickened and fibrous. There is no increase in the periportal fibrous tissue or any cellular infiltration of the interstitial tissue or capsule.

Pancreas: The parenchyma shows postmortem changes. The interlobular connective tissue, although not noticeably increased, contains in places a few lymphoid and polyblastic cells. The intima of a few of the arteries shows nodular fibrous thickenings.

Suprarenals: The blood vessels appear normal. The medulla shows postmortem changes.

Kidney: The intima of the larger and medium sized vessels is irregularly thickened and fibrous. There are a few small atrophic scars in the cortex. The capsules of a few of the glomeruli are thickened and in others there are well formed fibrous crescents. Many of these are in the glomeruli which are included in the scars mentioned above. A number of these scars are infiltrated with small mononuclear cells and contain many atrophic tubules. In

the cortex one also sees many small areas infiltrated with small mononuclear cells. Completely obliterated arterioles are seen near a few of the scars. In the normal appearing portion of the cortex a few of the glomeruli are very large. The tubules show no hypertrophy. The cells lining the secreting tubules are swollen and granular.

Further Study of the Brain and Spinal Cord.—After two and one-half weeks in 10 per cent. liquor formaldehydi the brain was removed. A transverse section through the midbrain above the level of the third nerve separated the cerebrum from the lower portions of the brain. Cross sections of the cerebrum, 1.5 cm. in thickness, were then made.

The brain was well fixed throughout and aside from the slight edema of the cortex, slight dilatation of the ventricles, the evident arteriosclerosis and slight local atrophy of the gray matter of the cortex nothing unusual was discernible.

Sections for microscopic study were taken from the various portions of the cortex and the basal nuclei. Similar sections of the first and second nerves were also made.

. Transverse sections were likewise made of the midbrain, pons, cerebellum, the medulla and from various parts of the spinal cord. Blocks of tissue were taken from all of these parts. They were carefully labeled, embedded, sectioned and stained. Each cranial nerve was removed into a separate bottle and was also sectioned and stained. All the sections were stained with hematoxylin and eosin.

Section 1 is taken from the cortex of the frontal lobe: There are a few small clumps of well preserved red cells in the subarachnoid space. Together with these there are scattered and small clusters of small mononuclear cells. These have the appearance of lymphocytes. There is no evidence of degeneration of the nerve cells or fibers in the gray or white matter. The perivascular spaces in the white matter are dilated and two contain a few small mononuclear cells like those in the meninges. The infiltration of the perivascular spaces and subarachnoid space is not marked, however, in this section. The blood vessels are all congested.

Section 2 is from the edge of the lateral ventricle in the occipital lobe: The perivascular spaces are distended. They contain fine pink staining granular material and in places a few small mononuclear cells. One contains a few polymorphonuclear leukocytes. About these perivascular spaces within the brain substances are a few round uniformly blue staining bodies, so-called myelin bodies. There is little evidence of proliferation of the endothelial lining cells of the perivascular spaces in either of these sections. The endothelial cells are flattened. Their nuclei are widely separated and vesicular.

Section 3 is through the velum interpositum: The nerve cells show little change of interest. Along the edge of the ventricle there are a few blue staining myelin bodies within the brain substance. The blood vessels are congested. The perivascular spaces are distended. Many of these are empty and there is no evidence of proliferation of their endothelial lining. A few, however, contain a small amount of pink granular material and others a few small mononuclear cells. Along the edge of the ventricle there are patches of edema. These patches are thickened and appear as small hillocks along the ventricle wall. The epithelial covering of the ventricle is absent over these hillocks.

Section 4 is through the cortex of the temporal lobe so as to include the main stem of the middle meningeal artery: There is marked fibrous and hyalin thickening of the intima of one side of this vessel. This thickening partially occludes the lumen. Under the pia mater and within the brain substance there are large numbers of the blue staining myelin bodies. The perivascular spaces are dilated and empty and there is no evidence of proliferation of the endothelial cells lining them.

Section 5 passes through the middle part of the ventricle and includes a considerable portion of the wall on each side. Under the pia covering of a part of the section there are many blue staining myelin bodies. The epithelium lining the ventricles is everywhere intact. The perivascular spaces are only partially distended, but the larger number are filled with small mononuclear cells (Fig. 1). Those containing a few of these cells are seen to be lined by a closely set row of low cuboidal shaped endothelial cells each of which has a sharply staining spherical shaped vesicular nucleus. A few of these endothelial cells are seen to be desquamating from this membrane into the space. The cells in the perivascular spaces are small and look very much like the endothelial cells proliferating along the wall of the space. They have a small and distinct mass of pink staining cytoplasm. The nucleus is vesicular and rich in chromatin. The brain substance of the whole section is definitely edematous, and there are patches where a few of the pink
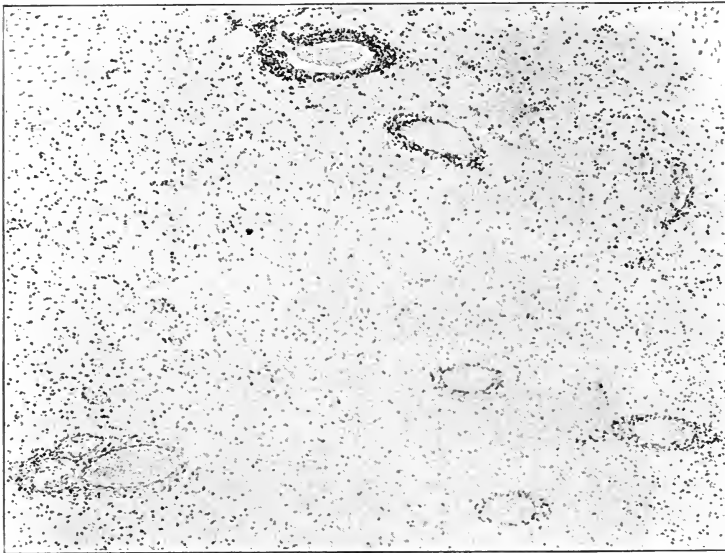

Fig. 1.—Section of the midbrain showing perivascular infiltration (Case 1).

staining axis cylinders are seen to be fragmented and curled. The nerve sheaths are filled with pink staining granular material. The nerve cells in many places are shrunken. The cytoplasm of all of them is pink and granular. Their nuclei are often irregular in shape and poorly defined from the cytoplasm about them.

Section 6 is from the brain stem at the level of the midpart of the pons: The perivascular spaces are everywhere distended. A few are empty. Others are filled with small and medium sized mononuclear cells. Very definite proliferation of the endothelium lining many of these spaces is discernible. In many places the nerve cells show degenerative changes like those in Section 5; in other places they do not. Their nuclei stain sharply and they are vesicular. The cytoplasm of all these cells appears to be slightly granular.

Section 7 is cut across the medulla. The changes are the same as those seen in the pons but they are not so extensive nor clearly defined. The process is apparently receding at this level.

Section 8 is a cross-section of the cervical cord. The subarachnoid space contains a few lymphoid-like cells. The endothelial lining cells show little evidence of proliferation. Many of the perivascular spaces are distended slightly and one or two in the anterior horn show endothelial hyperplasia and they contain a few small mononuclear cells. The brain tissue is not definitely edematous but the nerve cells show evidence of early degenerative changes like those in the pons and medulla.

Section 9 is taken from the middle part of the thoracic part of the spinal cord. Section 10 is from the lumbar region. Both these sections show slight changes like those in the cervical region, but in none of the cord sections are these alterations marked. On the other hand, a few myelin bodies are seen in all of these sections, especially in the white matter. Sections of the larger spinal arteries are not obtained. All of the penetrating vessels are congested.

Section 10 is a longitudinal section of the right ophthalmic nerve. The section includes the bulb and the distal end of the nerve. There are many blue staining myelin bodies along the periphery and in the mid-portion of the bulb and nerve. These are arranged in groups and rows between the fibers. The perivascular spaces are open but there are no evident inflammatory changes.

Section 11 is a longitudinal section of the left ophthalmic nerve. It presents the same general appearance as the right.

Section 12 is a longitudinal section of both optic nerves, the chiasm and the beginning of the optic tracts. Along the periphery of the section there are large numbers of myelin bodies. These are very numerous in places and their presence in one part of the nerve is associated with slight dilatation of the nerve sheaths. The perivascular spaces are open and in a few places their endothelial lining shows a definite increase in the number of cells. There are also a few clusters of lymphoid cells in the subarachnoid space. Other evidences of inflammation are wanting in this section.

Section 13 is a longitudinal section of the right oculomotor nerve. The section includes that portion of the nerve which lies within the cranial cavity. There are very few myelin bodies which were so common in the other two nerves described above. On the other hand there is a most striking infiltration of small mononuclear cells. These cells occur in large numbers about the larger blood vessels and in rows between the fibers in many places. There is little evidence of edema, but the axis cylinders are swollen in many places. Their outlines are sharp but irregular. The greatest amount of swelling in the axis cylinders corresponds to the areas of greatest cellular infiltration (Fig. 2).

Section 14 is a longitudinal section of the left oculomotor nerve and a cross section of the midbrain at this level. The brain stem shows most marked inflammatory changes. In many parts of the tegmentum the axis cylinders cannot be made out. Their sheaths are filled with pink staining granular material. The glia nuclei in all parts of the section stand out prominently. There is also a diffuse infiltration of small mononuclear cells in many places. The nerve cells are shrivelled in places, swollen in others. Their cytoplasm is granular and stains a slightly bluish pink color. The nuclei are shrivelled and often only half fill their original spaces in the cell. Many have indistinctly stained boundaries and are filled with bluish staining granules which are made out clearly only with the high power of the microscope. The perivascular spaces are distended and filled with small mononuclear and a few large clearer endotheliod cells. Their endothelial linings show proliferative and desquamative changes. The nerve is everywhere infiltrated with small mononuclear cells. These, as in the other nerve, occur in rows between the fibers and in clusters about the larger blood vessels. These clusters more than fill the interstitial tissue. They push aside the neighboring nerve fibers. No polymorphonuclear cells and very few myelin bodies are seen in this section.

The meninges about the nerve and brain stem contain large numbers of small mononuclear cells, and they are greatly distended in places by large clusters of these cells. There is also evident proliferation of the endothelial lining in a few places. This is not so marked, however, as in the perivascular spaces.

Sections 15 and 16 are longitudinal sections of the right and left trochlear nerves. They include those portions of the nerves which traverse the side of the brain stem. There are no myelin bodies. The nerve shows the same diffuse and patchy infiltration with small mononuclear cells as described in the case of the oculomotor nerves. The axis cylinders are swollen and in a few places are apparently fragmented. They have a pink color.

Section 17 is a cross section through the lower portion of the midbrain. It is similar to that at the level of the emerging roots of the third nerve.
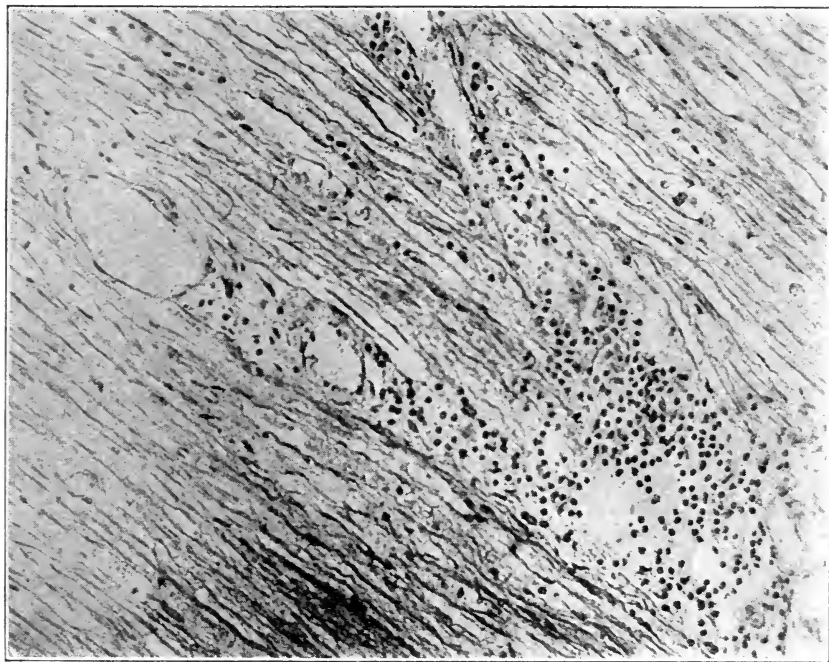

Fig. 2.—Section of the right oculomotor nerve showing inflammatory changes (Case 1).

Section 18 is a longitudinal section of the left trigeminal nerve. The section includes also a cross section of the neighboring part of the pons. The section is well stained. Along the periphery of the nerve there are many blue staining myelin bodies, but the nerve fibers show little evidence of swelling or degeneration and there is no cellular infiltration. Within the pons the nerve cells show little change of interest. The perivascular spaces about the veins are distended and contain a small amount of gelatinous pink staining material. One contains a few small mononuclear cells and there is evident proliferation of its endothelial lining. About this one there are also a few lymphoid cells scattered in the tissue. The glia nuclei stain sharply but do not appear increased. There is no cellular infiltration of the meninges nor endothelial proliferation.

Section 19 is a longitudinal section of the right trigeminal nerve. There are a few myelin bodies scattered among the fibers near the periphery of the nerve, but there is no evidence of inflammation or noticeable degeneration of the fibers.

Section 20 is a longitudinal section of the right abducens nerve. The endothelial cells lining the subarachnoid spaces appear in one place slightly more numerous than normal. There are no myelin bodies or other noticeable changes in this nerve.

Section 21 is a longitudinal section of the left abducens nerve. This section shows nothing of interest.

Section 22 shows the nuclei of the abducens nerves. A block containing these nuclei was cut from the fourth ventricle and sectioned transversely. The epithelial lining of the ventricle is intact. There is no marked evidence of edema of the tissue. All the perivascular spaces about the veins are distended. Their endothelial lining cells are greatly increased and they are filled with small mononuclear and a few large clear cells. Many of the nerve cells in the nucleus of the sixth nerve are well formed and normal appearing. Others are shrunken and have a deep bluish red granular cytoplasm in which the nuclei are made out with difficulty.

Sections 23 and 24 are made from the right and left facial nerves. The section includes the first 1 cm. of these nerves. These nerves, like the sixth nerves, show little of interest.

Section 25 is a longitudinal section of the left acustic nerve. It includes the first centimeter of the nerve as it emerges from the brain. Along the periphery of the nerve just beneath the pia mater and in places within it are a few blue staining myelin bodies. No inflammatory changes are seen in this nerve. The meninges are missing.

Section 26 is a similarly cut section of the right acustic nerve. The meninges are missing and there are no large blood vessels seen in the section. Along the periphery of the nerve and in places within it are numbers of myelin bodies. There is also a diffuse infiltration of small mononuclear cells. These occur in rows between the fibers. Definite changes cannot be made out in the poorly defined axis cylinders.

Section 27 is made through the pons at this level. It shows more perivascular involvement on one side than on the other. Sections of the roots of the glossopharyngeal nerves, vagus, accessory and hypoglossal nerves are seen in the several cross-sections of the medulla. Myelin bodies are absent in the roots of these nerves and none show any evident degeneration or inflammation.

Anatomic Diagnosis.—Acute polioencephalitis and acute myelitis, associated with wide spread inflammation of the meninges; neuritis of both oculomotor and trochlear nerves and the right acustic nerve; arteriosclerosis, general; local atrophy of the brain and cord; atrophy of the spleen; chronic inflammatory and arteriosclerotic nephritis; hypertrophy and dilatation of the heart; low grade prostatic hypertrophy; bronchopneumonia; cloudy swelling of the viscera; acute congeston of the viscera which is most marked in the lower part of the duodenum and the upper part of the jejunum.

Case 2.—A boy, aged 17 years, white, student at a school for boys in New Hampshire, was admitted, Nov. 4, 1919, to the surgical ward, service of Dr. Sachs, and immediately transferred to the medical ward into the service of Dr. Schwab.

Family History.—The family history is negative.

Past History.—The past history is negative.

Present Illness.—Previous to Oct. 5, 1919, the patient seemingly had been in perfect health. The first symptoms were vomiting and constipation. These were followed after several days by fever which at one time reached 103° F. At the time of this high fever and following it he noted difficulty in standing

when his eyes were closed. He tended at such times to fall always to the right. During this same time and for some time previous he also suffered transient attacks of diplopia

On account of these symptoms he was taken to the Peter Bent Brigham Hospital in Boston and admitted to the service of Dr. Harvey Cushing. A letter from there states that on admission (the date of which is not given) he had a subnormal temperature, nystagmus, hyperemia and edema of both optic disks, general muscular weakness and slight muscular atrophy, most marked in the lower extremities. Both Babinski's and Chaddock's reflexes were positive on the left and possibly also on the right. The tendon reflexes were brisk to exaggerated throughout; particularly in the left lower extremity. His speech was slurred and inarticulate. The nystagmus was marked when he looked to the right, left and upward. His sense of position was very poor and there was marked ataxia elicited with finger to nose, finger to finger and heel to shin tests.
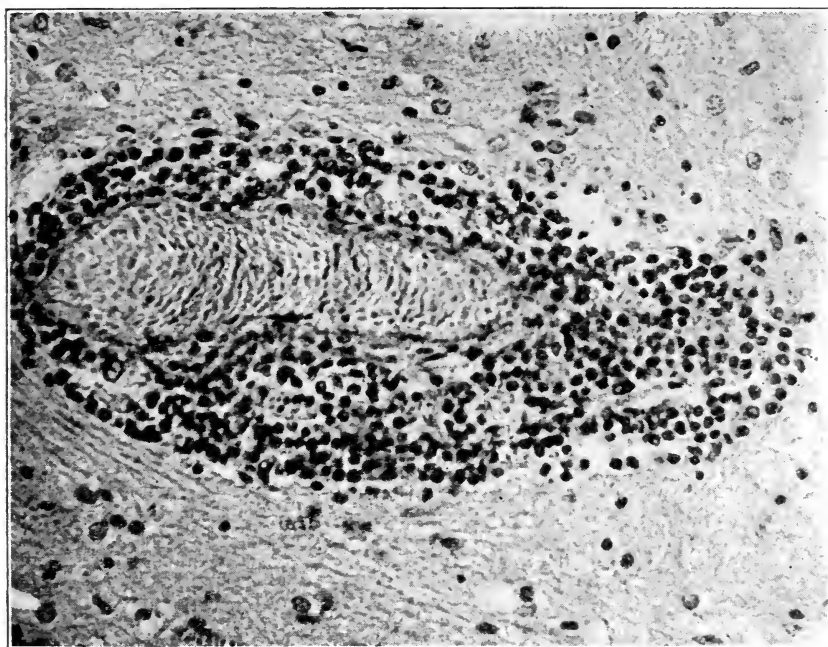

Fig. 3.—Congested vein in the midbrain from Case 2. The hyperplasia of the endothelial lining cells is shown along the wall of the vein and at the edge of the space. Desquamating cells may also be seen at several places along the peripheries of the space.

The leukocyte count was 16.000. The cerebrospinal fluid showed, however, only five cells and all cultures of it remained sterile. About a week after admission the patient began to complain of numbness and tingling sensations in his left leg, particularly in the foot. Later these symptoms developed in the right leg also. At this time the deep reflexes were not obtained at the ankle and they were very inactive at the knee. Plantar stimulation gave no toe response on the left and this response was questionable on the right. There was hyperesthesia on the left side well up to the second intercostal space and a somewhat similar condition on the right. The slight swelling of the optic disks still persisted. The paralysis of the lower extremities had increased so that he was unable to dorso-

flex the feet. The nerve trunks had become tender to pressure and Laseque phe-
nomenon was quite marked in both lower extremities. This was the condi-
tion at the time of his discharge from the hospital in Boston and just previous
to his admission here. The impression was that he was suffering from wide-
spread polyneuritis with considerably more involvement of the cranial nerves
than is usual.

Physical Examination and Clinical Course.—November 5. Patient is conscious
and fully orientated. His chief complaint is tenderness in both legs and pain
in his throat. He moans frequently, complains of being sleepy and his eye-
lids seem to drop and almost close at intervals. Breathing is shallow and
slow. There is no marked dyspnea. The left leg is completely paralyzed. The
right can be flexed at the knee but with difficulty. Slight pressure on the
peripheral nerve of both legs is painful. The patient's condition is such that
no further examination is deemed advisable just now. Tube feedings are
ordered.

5:30 p. m. (same day). The patient seems better and less anxious. The
left disk appears to be normal. The right is slightly hyperemic. The veins
are slightly tortuous. The edges are clearly seen. The picture suggests a
receding optic neuritis. There is bilateral insufficiency of the sixth nerves
which is more marked on the right side than on the left.

November 5. Dr. Dock examined the patient and noted that the heart and
lungs are negative and that the thyroid is slightly enlarged.

November 7. Plantar irritation causes plantar extension in the right foot
but no toe movements in the left. Later in the day a positive Babinski is seen
in both right and left feet. The knee kicks are absent. The abdominal reflexes
are also absent.

November 9. The patient is not as bright as usual. He remains alert for
only a very short time. He realizes that he has lethargic attacks and says
that he is not sleepy in the ordinary sense of the term but he just falls off.
The pupils are widely dilated. The speech is nasal, slurring and indistinct.
There is tenderness along the nerve trunks in the legs and slight tenderness
over the muscles.

November 12. The pulse is rapid. Analgesia is noted up as high as the
fourth dorsal segment. The arms are free. Both disks are hazy, the right
more than the left. There is a systolic murmur at the apex of the heart.
There is slight delirium and the lethargy is marked. Spontaneous vomiting
occurs during the day.

November 18. The patient is intolerant of the feeding mixture. The pulse
is poor. From this time on the patient became progressively weaker and weaker.

Jan. 5, 1920. Death occurs at 6:47 a. m.

The temperature during no time of the patient's stay in the hospital went
over 101 F. until the last three days, when it began to ascend and reached a
height of 108.5 F. at the time of death. The pulse at all times went up and
down with the temperature.

Laboratory Findings.—Urine was examined frequently. Its specific gravity
varied between 1.013 and 1.026. There was never any sugar but traces of
albumin were present at times.

The blood counts were as follows: Nov. 7, 1919, leukocytes, 12,200; Novem-
ber 16, leukocytes, 8,600; December 30, leukocytes, 19,400.

The spinal fluid was taken Nov. 14, 1919. There were six lymphocytes per
c.mm. The pressure was normal. The Pandy test was positive. The Wasser-
mann was negative. Smears, cultures and animal inoculations yielded nothing.
The colloidal gold test was 5554320000. The Wassermann test of the blood was
negative. Cultures of the blood taken Dec. 30, 1919, and Jan. 4, 1920, were
sterile.

The electrocardiogram suggested a left ventricular preponderance with a
vertical heart.

Stereoscopic roentgenograms of the skull taken Dec. 2, 1919, showed nothing unusual.

Clinical Diagnosis.—Lethargic encephalitis, associated with a general polyneuritis.

The necropsy was performed Jan. 5, 1920, at 8:30 p. m. or about two hours after death.

Necropsy Findings.—The body is that of a poorly nourished boy. It measures 175 cm. in length and weighs 36 kg. The pupils are equal; openings measure 4 mm. in diameter. There is a hemorrhage into the sclera of the right eye near the inner canthus. The skin has a pale color. The lips are pale. The teeth are in good condition and they are slightly prominent. The hair is thin. There is a needle prick near the midline of the back and just above the level of the third lumbar spine. The external genitalia appear normal. The body is warm.

There is very little subcutaneous fat. The trunk is long. Both lungs collapse when the chest is opened. The pleural cavities are everywhere smooth and dry. The thymus is small and firm. Small islands of parenchyma are plainly visible in the fibrous tissue of which it is largely composed.

The heart weighs 210 gm. and is filled with fluid blood. Aside from a few fatty placques in the aorta and slight dilatation of both the mitral and tricuspid rings, little of interest is noted. The heart was saved intact and was given to the "heart station" for special study.

Lungs: The left lung weighs 185 gm.; the right weighs 435 gm. The left lung is doughy in consistency. The lower lobe is slightly injected. The cut surface is everywhere dry, and the alveoli are partially collapsed. The upper lobe of the right lung has the same appearance as that of the left while the more dependent portions of the middle and all of the lower lobe are firm and soggy in consistency and their cut surfaces are moist. Frothy fluid flows from the bronchi and alveoli and it is studded with numbers of small bluish red granular raised patches. The dependent portions of the middle lobe have the same appearance as that of the lower lobe excepting that the consolidated areas are smaller and not so numerous. The peribronchial glands are slightly enlarged, deeply pigmented, and one of them on the right side contains a small fibrous scar.

Spleen: Weighs 180 gm. and measures 14.5 by 7 by 3.2 cm. The capsule is everywhere smooth, thin and translucent except for a few tiny fibrous tags near its upper pole. The organ is firm and slightly rubbery in consistency, and its cut surface has a deep bluish red color. Blood flows from this surface. The larger arteries can be made out easily. Their walls do not appear to be thickened. The malpighian corpuscles are not seen in the artificial light.

Liver: Weighs 1,380 gm. and measures 30 by 21 by 6.5 cm. The capsule is everywhere smooth, thin and translucent. Through it the deeply congested centers of the lobules are easily seen. These lobules stand out clearly on the cut surface. Their centers are deeply congested and appear slightly sunken below the grayish brown boiled appearing peripheries.

The gallbladder contains a small amount of viscid greenish black bile. Its walls are thin and delicate.

Stomach: The pylorus and antrum are firmly contracted. The fundus contains about 200 c.c. of a black colored fluid which contains a few small blood clots. The mucous membrane is well preserved.

Duodenum: It contains bile stained fecal matter. The mucous membrane is congested throughout and there are numerous small hemorrhages into it. Bile can be made to flow readily from the papilla of Vater.

Pancreas: Appears normal in form and consistency, but it is small. It weighs 50 gm. Little or no fat surrounds it.

Suprarenals: Are elongated in the vertical direction. The cortices have a grayish yellow color. The medullae are narrow and congested.

Kidney: The right weighs 110 gm. and measures 10.2 by 6 by 3 cm. The left weighs 120 gm. and measures 10.5 by 5.7 by 3.75 cm. The capsules strip easily. There is slight evidence of fetal lobulation. The stellate veins are congested. The cortices have a grayish red color. On section, the medullae are found to be congested. The interlobular vessels of the cortices are congested which makes the gray columns stand out prominently. The striations are straight. The glomeruli are seen as both tiny gray and red pinpoint size dots. The cortices each measure 6 mm. in thickness. The right ureter and the bladder are slightly dilated. No evidence of obstruction is made out, however. The prostate and seminal vesicles appear normal. The rectum appears normal.

Intestines: The mucous membrane is well preserved everywhere, except that of the duodenum. The Peyer's patches and solitary follicles are not enlarged. The mesentery is almost free from fat. The lymph glands in it are slightly enlarged. The retroperitoneal glands appear normal.

Aorta: The intima is smooth. It is elastic.

Brain: (See below.)

The neck organs, spinal cord and peripheral nerves are not removed.

Microscopic Examination.—Lungs: Sections from the lower right lobe of the right lung show the smaller bronchi filled with pus and surrounded by an area of distended and pus filled alveoli. Skirting these foci and isolated in other parts of the section there are groups of alveoli filled with well preserved red cells. The blood vessels are congested and all of the otherwise empty alveoli contain a few polymorphonuclear, large mononuclear and red cells. Sections from other lobes show nothing of interest.

Spleen: The malpighian corpuscles are small, uniformly cellular and sharply circumscribed from the greatly congested pulp sinuses. The endothelial cells lining the pulp spaces appear to be increased. The nuclei are spherical in shape, vesicular and they stain sharply. Within the pulp spaces there is a noticeable but slight increase in the number of polymorphonuclear and small mononuclear cells.

Liver: The parenchymatous cells are swollen and granular and those in the centers of the lobules contain many small vacuoles.

Pancreas: Sections from head, body and tail show nothing unusual.

Kidney: The cells lining the secreting tubules are irregularly swollen and granular.

Duodenum: The solitary follicles appear slightly enlarged and they are uniformly cellular. The mucosa is densely infiltrated with polygonal shaped cells and the outer ends of the villae are congested and hemorrhagic.

Stomach: Shows nothing of interest.

Mesenteric Lymph Nodes: The sinuses are slightly distended and empty. There is no evident hyperplasia of the parenchyma.

Urethra: There is a scattering of lymphoid-like cells in the prostatic urethra near the bladder orifice.

Brain: The whole of the cerebral cortex is edematous, and the subdural space contains about 75 c.c. of what appears to be a slightly turbid fluid. Blood has escaped into this from the cut vessels of the dura. Smears of this fluid show no increase in cells other than those of the blood. The blood vessels of the brain are slightly congested and there is definite clouding of the pia arachnoid along the fissures of the superior portions of the cortex.

Spinal Cord of the Cervical Region: A small part is removed from the canal. There is no bulging of the cord substance at the point of section. The whole cord is congested. The boundaries between the gray and white matter can be seen readily.

The brain and cord are placed in liquor formaldehydi.

After three weeks' fixation the brain is sectioned. The midbrain is cut through and the pons, medulla and cerebellum removed. The cerebrum is cut into cross sections of 1 cm. in thickness and pieces are taken from various

regions for microscopical study. Similar sections are made from various parts of the brain stem and the cerebellum. The cranial nerves are also removed, marked, sectioned and stained. The sections are stained with hematoxylin and eosin.

Microscopic Study of Sections of the Brain and Cord: Section 1 is a longitudinal section of the bulb and a portion of the right ophthalmic nerve. There is definite edema of the bulb along one side with a deposit of pink staining granular material between the fibers. The meningeal vessels are congested but there is no cellular infiltration of the meninges in this region. The penetrating vessels are also congested but there is no distention or infiltration of their perivascular spaces. The endothelial lining of these spaces shows no evidence of proliferation.

Section 2 is a similar section of the bulb and a part of the left ophthalmic nerve. The section shows nothing of interest aside from the congestion of the meningeal and larger penetrating vessels. This congestion is largely restricted to the veins.

Section 3 is a frontal section of both optic nerves and the optic chiasm. The larger blood vessels are congested and all the perivascular spaces are distended. The endothelial cells lining these spaces show marked proliferation and many of the spaces are filled with small mononuclear cells.

The subarachnoid space covering the nerve is distended and contains many small mononuclear cells. The nerve tissue immediately beneath the meninges appears edematous.

Section 4 is a longitudinal section of the right oculomotor nerve for a distance of 1.5 cm. outward from the brain. The section is longitudinally cut. The perivascular spaces of the larger blood vessels are filled with small mononuclear cells. Similar cells are also seen in many parts of the section between the nerve fibers. The axis cylinders are seen in many places. A few appear swollen but none are degenerated. The nuclei of the Schwann sheath cells appear large and more prominent than normal. The subarachnoid space is distended and contains many small mononuclear cells.

Section 5 is a longitudinally cut section of the left oculomotor nerve. This nerve shows the same changes as the other except that the infiltration is more marked under the meningeal covering than on the right side. The meninges are present in this section.

Section 6 is a longitudinal section of the right trochlear nerve. This nerve is densely infiltrated everywhere with small mononuclear cells. Large numbers of these cells are lined in rows between the fibers and they occur in clusters about the larger blood vessels.

The subarachnoid about the nerve is distended and filled with small mononuclear cells. There are also several larger bodies in this space and attached to its walls. These bodies are covered with well formed endothelial-like cells and are composed within of concentric rings. The whole body may stain pink or have a pinkish blue color. A few have a circular or irregular blue staining central mass. These bodies look like the endothelial pearls so common in endothelioma of this region. Aside from these changes the subarachnoid space shows no changes. There is no evidence of proliferation of the cells lining it.

Section 7 is a longitudinally cut section of the left trochlear nerve. This nerve shows the same perivascular changes as the one of the other side but there are very few cells scattered between the fibers. On the other hand, many of the axis cylinders of this nerve cannot be seen. Many of the nerve sheaths contain pink staining granular material. This is also seen between many of the fibers. The meninges are not present, except for one small tag. This tag contains many small mononuclear cells.

Section 8 is a cross section of the pons at the level of the trigeminal nerve. The subarachnoid space is everywhere distended and contains many small mononuclear cells and masses of pink staining granular material. The endo-

thelial lining of this space appears normal. There is no evident proliferation. The blood vessels are greatly distended with blood and their walls contain large numbers of small mononuclear cells. There are no definite hemorrhages but here and there well preserved and shadows of red cells can be seen scattered in the open space. This space also contains a few large clear endothelial-like cells.

Throughout the tegmentum and pons proper the blood vessels are congested. Many of the perivascular spaces are filled with well preserved red blood cells which extend also out into the brain tissue in many places. Others of the perivascular spaces show simply proliferative changes of their endothelial lining cells, while others are distended with large numbers of small mononuclear cells. The proliferative changes are manifested by a great increase in the nuclei of lining cells. These cells are small and cuboidal in shape. In many of these spaces cells may be seen to be desquamating into the space from the lining membrane. All of the cells in the spaces have the same appearance as those budding out from the lining.

The brain substance shows various changes. In places it appears normal. In other places it is more open and there is a deposit of pink staining granular material between the fibers. There are also places in the tegmentum where the glia nuclei appear increased and small mononuclear cells are seen scattered in the tissue along the capillaries and smaller blood vessels.

On the other hand, the nerve cells in this section show no marked degenerative changes. In a few areas they appear more granular, their nuclear outlines are not so sharp and a few appear slightly smaller than normal. There is no neuronophagia.

Section 9 is a longitudinal section of the right abducens nerve. The meninges have been torn away. Within the nerve small mononuclear cells are seen in numbers between the fibers.

Section 10 is a longitudinal section of the first centimeter of the left abducens nerve. The meninges are missing. The nerve shows nothing of interest.

Section 11 is a longitudinal section of the first 1.5 cm. of the right facial nerve. Small mononuclear cells are seen clustered about the larger blood vessels and in places between the fibers. Along one edge of the nerve there is a pink staining granular deposit within a few of the nerve sheaths and between the nerve fibers. The subarachnoid space is distended and contains a scattering of small mononuclear cells. The blood vessels are congested.

Section 12 is a longitudinal section of the first centimeter of the left facial nerve. The subarachnoid space is distended and it contains a scattering of small mononuclear cells. The nerve proper shows no changes except for the presence of a few small mononuclear cells among the more peripherally placed fibers.

Section 13 is a longitudinal section of the first centimeter of the right acustic nerve. This nerve shows an extensive perivascular and diffuse infiltration of small mononuclear cells. Otherwise it shows little of interest.

Section 14. A similar picture is seen in this section, a longitudinally cut section of the first centimeter of the left acustic nerve.

Section 15 is a cross section of the medulla at the level of the hypogastric and glossopharyngeal nerves. The whole brain stem at this level appears slightly edematous. The blood vessels are congested. The perivascular spaces are distended. Those about the arteries are in part empty. Others contain a small amount of pink staining granular material. The endothelial lining cells of these spaces about the arteries are not increased in number. This is not true, however, for the veins. The endothelial cells lining the perivascular spaces are increased. Many of the spaces are filled with small mononuclear cells. The subarachnoid space is distended slightly. The blood vessels are congested and the space contains a scattering of small mononuclear cells. These are seen in the pia covering the roots of both the glossopharyngeal and hypoglossal nerves, but the nerves themselves show nothing unusual.

Within the brain the most pronounced changes are seen about the larger veins in the raphé, in the formatio reticularis and in the dorsal nuclei. Throughout the whole of the section the nerve cells show changes. These consist of shrinking in the size of the cells and a decrease in staining properties of the nuclei. The cytoplasm is granular and the nuclear cytoplasmic boundaries are not sharply defined.

Section 16 is a cross section of the medulla at the level of the hypoglossal and the vagus nerves. The alterations in this section are similar to those in Section 15, excepting that the perivascular infiltration is more marked. Endothelial proliferation and cellular infiltration is seen also in the perivascular spaces about the larger arteries. The nerve roots are uninvolved and there is no striking evidences of degeneration. The nuclei of the Schwann sheath cells of a few appear prominent.

Section 17 is a cross section of the upper end of the cervical cord. The changes in this section are like those in the medulla. The meningeal changes are most marked on the anterior surface and in the anterior central fissure. The perivascular changes are also more pronounced about the vessels penetrating in this region. The nerve roots as above are not definitely involved and there is no striking evidence of degeneration of the nerve cells in any part of the section.

Section 18 is made through the cortex of the frontal lobe. The subarachnoid space is slightly distended and contains a few small mononuclear cells. The outer edge of the gray matter is slightly edematous. There are no marked perivascular changes, however, of any kind. The blood vessels are congested.

Section 19 is made from the postparietal region of the cortex. The changes in this section are similar to those in Section 18.

Section 20 is a section through the corpus callosum. Aside from congestion of the blood vessels nothing of interest is seen.

Section 21 is made through the middle of the optic thalamus and the wall of the fourth ventricle of the right side. The epithelial lining of the ventricle is intact. The tissue beneath it is edematous and the capillaries are congested. Throughout the whole section the perivascular spaces about both the veins and the arteries are distended. All of these vessels are congested. There is no proliferation of the endothelial lining of the spaces about the arteries. These spaces are in part empty. Others contain small amounts of pink staining granular material. The perivascular spaces about the veins show marked changes. They are lined by cuboidal endothelial cells which are being desquamated in part into the space. The spaces are filled with small mononuclear cells. The brain tissue about each of these spaces is edematous. The nerve cells in this region show, however, little of interest except that their cytoplasm is slightly more granular than normal.

Section 22 is made through the thalamus, internal capsule and lenticular nucleus of the opposite side at the same level as the preceding section. The changes in the thalamus are similar to those of the opposite side. The most intense changes in this section are located in the internal capsule. The whole tissue is edematous. All of the perivascular spaces are greatly distended and filled with cells. Their endothelial lining cells show marked proliferation. The glia nuclei stand out sharply in the section and appear increased and the tissue about many of the perivascular spaces is infiltrated with small mononuclear cells. Many of the axis cylinders, however, can be seen to be definitely intact. Similar changes are seen along the neighboring edges of the lenticular nucleus. The greater part of this nucleus, however, shows no changes aside from congestion of its blood vessels.

Section 23 is through the septum pellucidum including the corpus callosum, the convolutions at the bottom of the median longitudinal fissure and a part of the wall of the third and both lateral ventricles. The tissue beneath the floor of the ventricles shows diffuse and focal areas of edema A few of the perivascular spaces in the white matter are distended. Their endothelial

lining cells are increased and they contain a few small mononuclear cells.

Section 24 is a cross section of the brain stem at the level of the substantia nigra. The changes in this section are like those in the pons below and in the internal capsule above. The perivascular spaces are distended and lined by closely set cuboidal cells. These are filled with small mononuclear cells (Fig. 3). The tissue throughout the whole section is edematous. This is most marked about the larger blood vessels and in this region there are also a few scattered small mononuclear cells. The meninges are also infiltrated with many small mononuclear and a few larger endothelioid cells. The blood vessels everywhere are congested and in places within the tegmentum there is a deposit of pink staining granular material between the nerve fibers. The changes in the nerve cells are not in any place of an extreme degree. In places they are of normal size but stain palely. In other places they are slightly shrunken; their cytoplasm is granular, and their nuclei stain poorly. About the aqueduct of Sylvius they are normal in size, stain sharply and are filled with brown pigmented granules.

Section 25 is similar to Section 24, but is taken at a slightly lower level. The changes are also similar to those of the preceding section, except that a number of endothelial pearls are attached to the wall of the subarachnoid space. These are like those seen in the meninges enclosing the right trochlear nerve, Section 6.

Sections 26 and 27 are sections of the upper and middle portions of the pons. These sections show changes similar to those seen in Sections 24 and 25.

Section 28 is from the dentate nucleus of the cerebellum. A few of the perivascular spaces are distended. Their endothelial lining cells are increased. There is no evident edema and no marked evidence of cellular or fibrillar degeneration.

Section 29 is through the optic tract and the posterior commissure. A few of the periportal spaces show proliferation of their endothelial lining and a few of these contain a number of small mononuclear cells. The subarachnoid space is distended and contains a scattering of small mononuclear and red cells.

Anatomic Diagnosis.—Acute polioencephalitis and acute myelitis, associated with a localized and widespread inflammation of the meninges; neuritis of the optic, oculomotor, trochlear, trigeminal, abducens, facial and acustic nerves; acute and chronic passive congestion of the viscera; acute cerebral edema; acute congestion and hemorrhage into the mucosa of the duodenum; hemorrhage into the conjunctiva of the right eye; emaciation; acute localized unilateral bronchopneumonia; acute splenic tumor; cloudy swelling of the viscera; fatty changes in the liver; healed fibrous scar, right peribronchial lymph gland; chronic prostatic urethritis.

CASE 3.—H. H. D., male, white, druggist, aged 24 years, was admitted Dec. 13, 1919, from an ambulance to the service of Dr. Schwab.

Present Illness.—He has been sick since Monday, December 8, and his first symptoms were inability to see plainly and he had to puzzle over things he said. His temperature, he thinks, began to rise Tuesday morning. Tuesday night it was 101 F. With the temperature he began to feel drowsy. He gives no history of having had influenza or anything like it. His family and past history are entirely negative. Previous to this time he has always been healthy.

Since the beginning of his present illness he has continued to work in the store until this morning. Since Tuesday he has had fever and headache and since yesterday he has had transient attacks of diplopia. His appetite is fair. There has been no nausea or vomiting.

Physical Examination.—The patient is a young man. He lies quietly in bed. The face is masklike and expressionless. The skin is hot and dry. He answers questions promptly and relevantly, but is slightly disorientated. He

thinks he is in the Dix Hospital and that the day is Monday. The scalp is clean. There is beginning temporal baldness. The hair is light brown in color.

Eyes: The pupils show nothing unusual. They react poorly to light. This is more noticeable in the right than in the left eye. There is marked weakness, especially of the left eye, to external rotation. There is no diplopia at the present time There is marked weakness of conveyance and the accommodation reactions are poor. On looking either to the right or left, there is nystagmus to that side. On looking upward the nystagmus is either vertical or rotary.

Ears and Nose: Negative. Hearing is not tested.

Mouth: The breath is foul, otherwise the mouth shows nothing of interest. There is a questionable right facial weakness. The tongue protrudes in the midline.

Neck: There are a few palpable glands (also in the axilla and groin). The thyroid is moderately and generally enlarged.

Heart, lungs and abdomen appear to be normal. The respirations are 26. Pulse is 82. Temperature is 101 F.

The arms and legs have normal strength. There is slight tremor of the extended hands. Biceps and triceps jerks are present and equal. Knee jerks are present, equal and increased. There are no sphincter disturbances and no rigidity of the neck. There are no Kernig and no pathologic toe signs.

Fundi: The disks are hyperemic and elevated, especially the left. Their margins are obliterated.

Clinical Course.—Dec. 14, 1919: The patient is slightly more delirious than yesterday. There is slight ptosis of the right eye.

December 15: There is slight spasticity of both arms. All the tendon jerks are increased. There are bilateral pseudoptosis and weakness of the sixth and seventh nerves and evident hallucinations. A lumbar puncture is made.

December 16: A second lumbar puncture is made. Patient appears much worse. There is marked delirium. Arsphenamin, 0.3 gm., is given intravenously. There is no reaction.

December 19: The patient is again worse. Divergent strabismus is present. Examination by the otologic clinic shows bilateral chronic otitis media. The respirations are increased and bubbling râles are heard over the right back. The pulse is 120. Patient is in deep stupor. He dies with respiratory failure at 9:58 a. m.

The blood pressures throughout his illness were as follows: December 13, 118/87; December 14, 127/92; December 15, 155/105; December 16, 172/112; December 17, 185/125; December 18, 165/90.

Stereoscopic roentgenograms of the skull showed nothing unusual.

Laboratory Findings.—The urine never showed anything unusual. Blood: erythrocytes, 6,500,000; hemoglobin, 85 per cent. Leukocytes: December 13, 8,000; December 14, 12,000; December 15, 14,000; December 16, 20,000; December 17, 24,000; December 18, 20,000. The differential count showed from 60 to 89 per cent. polymorphonuclear cells. Blood cultures on three occasions were always sterile. Blood Wassermann was negative.

Spinal Fluid: December 15: Clear and under normal pressure. Pandy is markedly positive. The gold curve is 0122100000. The cell count is 0. Wassermann test is negative.

December 16: It is straw colored and hemorrhagic and under normal pressure. There are 4,000 red blood cells and 28 leukocytes per c.mm. The Pandy test is markedly positive. The gold curve made with centrifuged fluid is 0012100000. The Wassermann test is negative.

The electrocardiogram was normal with a rate of 120.

The temperature ranged between 101 and 102 F.; pulse, between 100 and 115; respirations, between 26 and 32.

Clinical Diagnosis.—Acute lethargic encephalitis; partial paralysis of the third, sixth and seventh nerves; nystagmus; optic neuritis, bilateral; otitis media, chronic and bilateral; terminal bronchopneumonia.

The necropsy was performed by Dr. Walsh, one and one-half hours after death. Permission was granted for an examination of the head only. The brain was examined by myself.

Necropsy Findings. — The calvarium appears to be normal. There is a slight excess of fluid in the subdural space. The brain is deeply congested everywhere, but there is only a small amount of edema of the cerebral cortex. There are, on the other hand, evidences of small fresh hemorrhages into the subarachnoid space of the cerebrum. These are located along the larger veins and give a fuzziness to the outlines of these vessels.
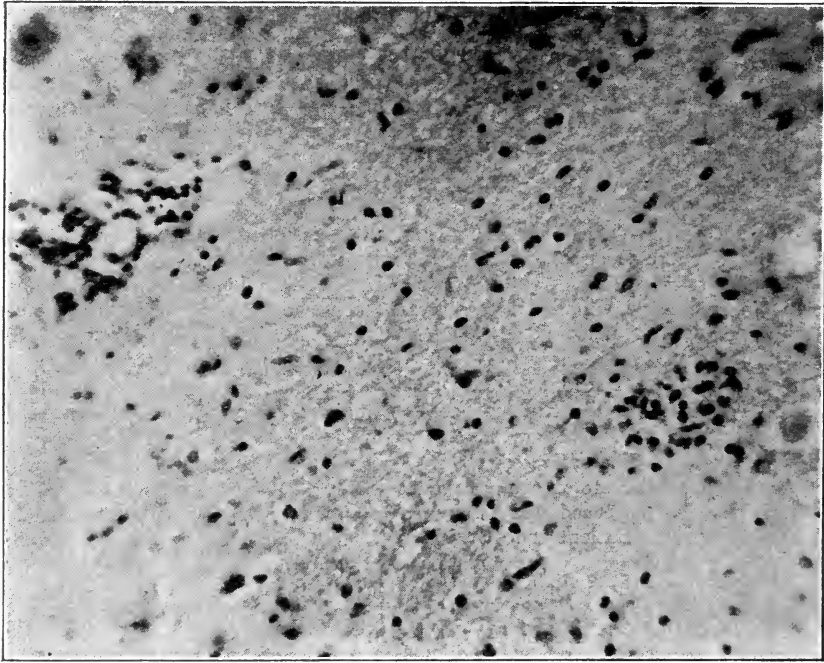

Fig. 4.—Section of the substantia nigra, Case 3, showing diffuse and focal infiltration with small mononuclear cells. A polymorphonuclear leukocyte is seen in the focal lesion on the left side of the picture.

The brain is removed to liquor formaldehydi to be examined later. The hypophysis appears to be normal. Aside from congestion the cerebral blood sinuses appear normal. The optic disks are slightly but definitely swollen and congested.

Formaldehyd Fixed Brain: The veins of the cerebrum are greatly congested. Many show the same fuzziness of outline as was noted in the freshly removed brain. The meninges in the depth of the fissures are cloudy. The brain stem has been cut across at a point just below the level of the olive. There is no bulging of the brain substance at this point of section. It is congested, however, but the outlines of the gray and white matter are distinct. The brain is sectioned in a manner similar to that used for the study of the other cases.

The penetrating vessels are everywhere congested. This congestion is most marked about the slightly dilated ventricles. The ventricle lining otherwise appears smooth. The choroid vessels aside from congestion appear normal. The congestion is brought out well in the blocks of the tissue removed to 80 per cent. alcohol. The gray matter of the thalamus, midbrain, pons and medulla appear also slightly more granular than normal.

Microscopic Examination of Sections.—Sections 1 and 2 are longitudinally cut sections of the right and left ophthalmic nerves. The bulb is not included. These sections aside from congestion of the blood vessels show nothing unusual.

Section 3 is a longitudinal section of both optic nerves and the chiasm. The subarachnoid space is distended and contains a scattering of small mononuclear and a few larger endothelial cells. The blood vessels in all parts of the section are congested. The tissue immediately beneath the pia mater is edematous. Many of the perivascular spaces throughout both nerves and the chiasm are filled with small mononuclear cells. This tissue about this space is edematous and also contains a few small mononuclear cells scattered in it between the nerve fibers. The endothelial cells lining the spaces are increased.

Section 4 is a longitudinal section of the first centimeter of the right oculomotor nerve. There are a few lymphoid cells scattered in the meninges and about one of the vessels in the nerve.

Section 5 is a longitudinal section of the first centimeter of the left oculomotor nerve. This nerve shows changes similar to that of the other.

Section 6 is a longitudinal section of the right trochlear nerve. No changes of interest are seen in this section.

Section 7 is a longitudinal section of the left trochlear nerve. In one place there are a few small mononuclear cells scattered between the fibers.

Sections 8 and 9 are longitudinal sections of the right and left trigeminal nerves. In small areas of both nerves there are a few small mononuclear cells scattered between the fibers and about the larger blood vessels. Otherwise these nerves show nothing of interest.

Sections 10 and 11 are longitudinal sections of the two abducens nerves. The nerves appear normal.

Sections 12, 13, 14, 15 and 16 are longitudinal sections of the seventh and eighth nerves. There are a few small mononuclear cells clustered about a blood vessel in the sections of both the right and left acustic nerves. No marked changes are seen in either of the facial nerves. The nerve roots of the glossopharyngeal, vagus and hypoglossal nerves are seen in sections of the medulla. They show nothing of interest excepting congestion of their blood vessels.

Section 17 is made through the posterior parietal region of the cortex. The subarachnoid space contains a few small mononuclear cells. The blood vessels of the meninges and brain are congested. The endothelial cells lining one of these spaces are increased.

Section 18 is a section through the left occipital lobe. It extends from the cortex to the ventricle. The vessels of the brain and meninges are congested and there are several small hemorrhages into the meninges. The tissue in the wall of the ventricle is edematous. In places it is thrown up into small hillocks which project into that cavity. The epithelial lining of the ventricle is missing over these hillocks. The perivascular spaces of the blood vessels are distended but empty. The endothelial cells lining these spaces show no change. The subarachnoid space is distended and filled with pink staining granular material and a few scattered small mononuclear cells.

Section 19 is through the middle part of the thalamus and the wall of the fourth ventricle. The whole of the thalamus is edematous and there is a deposit of pink staining granular material in the tissue meshwork. There is marked proliferation of the perivascular endothelium of the veins and these perivascular spaces are filled with cells. The capillaries are congested and there is a diffuse infiltration and in places, small clusters of mononuclear cells in the tissue. The cells in these small clusters lie in the meshes of the

tissue which shows no evident necrosis. The glia nuclei throughout the section are prominent and in places appear slightly increased in number. Most of the nerve cells are shriveled and have an open space about them. Mononuclear cells have invaded many of these spaces. The nuclei of these nerve cells is not clearly defined and they stain poorly. In a few they have shrivelled and become picnotic and there is an open space in the cytoplasm along the side of a number of this latter type. The cytoplasm is densely granular. There is no evident neurofibrillar structure.

Section 20 is through the septum pellucidum and cortex of the brain at the bottom of the median longitudinal fissure. The blood vessels are congested. The subarachnoid space of the meninges is dilated and it contains large numbers of small mononuclear cells.

Section 21 is a section through the thalamus, internal capsule and lenticular nucleus on the side opposite from that which Section 20 is taken and at a higher level. The blood vessels are congested. The perivascular spaces are dilated and empty. There is no hyperplasia of their endothelial lining cells.

Section 22 is of the cerebral cortex at the same level as Section 21. The meningeal blood vessels and brain vessels are congested. The subarachnoid space is dilated and contains a small amount of pink staining granular material and a few small mononuclear cells. The perivascular spaces are dilated and empty.

Section 23 is a cross section through the midbrain at the level of the substantia nigra. The changes are localized to the tegmentum. There are no perivascular or other evidences of change in the cerebellar peduncles. In the tegmentum the perivascular spaces are dilated. There is marked proliferation of their perivascular endothelium and they are filled with cells. The brain tissue about these spaces is edematous and in many instances it is also being invaded by small mononuclear cells. In places in the substantia nigra mononuclear cells are found and there are several small clusters of these cells lying in open spaces in the tissue. The nervous tissue in these areas is undergoing necrosis; here and there a few polymorphonuclear leukocytes are scattered in them (Fig. 4). The nerve cells in most parts of the section show no changes except that a few appear granular and slightly shrivelled. The aqueduct of Sylvius is slightly dilated and it contains a small amount of pink staining granular material. The epithelial lining is everywhere intact.

Section 24 is through the middle of the pons. The perivascular spaces in all parts of the section are distended. Those about the veins are filled with cells and their endothelial lining shows marked proliferation. The greater part of the tissue of the tegmentum appears edematous and there are areas in the tegmentum diffusely infiltrated with small mononuclear cells. The nuclei of the pons proper show little change while in the tegmentum all of the nerve cells show evidences of degeneration. They are shriveled. Their cytoplasm is granular. Their nuclei are either shriveled or they stain palely. In the motor nucleus of the fifth nerve on one side the cells are shriveled and small mononuclear cells are found in the open space about many of them. The glia nuclei are apparently not increased.

Section 25 is through the lower end of the pons and the nucleus of the abducens nerve. The changes in this section are similar but not so advanced as in the other. Besides moderate perivascular changes there are many tiny hemorrhages into the tissue and into a few of the perivascular spaces of the tegmentum. These are especially noted in the more dorsal part and in the median raphé. The nerve cell changes are not conspicuous. The nerve cells of the abducens and facial nuclei are not shriveled but their cytoplasm appears granular and there are a few capillary hemorrhages in one of the nuclei of this nerve.

Section 26 is a section through the cerebellar cortex. The Purkinje cells appear granular and their nuclear cytoplasmic boundaries are not distinct. The meninges show no changes.

Section 27 is another section through the cerebellar cortex. The Purkinje cells appear normal. There are a few mononuclear cells in an otherwise partially closed subarachnoid space.

Section 28 is through the cerebellar cortex and the dentate nucleus. The cortical cells appear normal. The perivascular spaces in the medullary substance and in the dentate nuclei are dilated and there is slight evidence of proliferation of their lining endothelium.

Section 29 is through the nucleus of the trochlear nerves. It includes only the dorsal part of the midbrain at this level. It shows changes like those in Section 23.

Section 30 is a cross section of the medulla at the level of the middle of the olive. The choroid plexus appears normal. It is not congested. The cells lining the ventricle are everywhere intact. The brain tissue is not edematous. The meningeal and penetrating veins are congested. The endothelial cells lining a few of the perivascular spaces show hyperplasia and a few of the perivascular spaces contain four or five cells. The cytoplasm of the nerve cells is slightly granular, otherwise the tissue appears normal.

Sections 31, 32, 33 and 34 are sections of the pons, the left trochlear nerve, the right oculomotor nerve and the left ophthalmic nerve. These sections are stained by Weigert's method. No evidence of degeneration is seen in any of the sections. The only change is a slight brown color in the tissue between the nerve fibers of the tracts in the tegmentum of the pons.

Anatomic Diagnosis.—Acute polioencephalitis associated with an extensive low grade inflammation of the meninges; neuritis of the optic nerves; neuritis of both oculomotor, left trochlear, both trigeminal and both acustic nerves; acute cerebral congestion and edema; bilateral choked disks.

DISCUSSION

The three cases described above present the clinical and pathological picture that is now known as diagnostic of "encephalitis lethargica." The lesions noted in the central nervous system of these cases, like the ones previously described by V. Economo,[1] Wilson,[2] Marinesco,[3] Marie and Trétiakoff,[4] Bassoe,[5] Bassoe and Hassin,[6] Calhoun,[7] Netter,[8]

1. Von Economo, C.: Encephalitis Lethargica, Wien. klin. Wchnschr. **31:** 850, 1918.

2. Wilson, S. A. K.: Epidemic Encephalitis, Lancet **2:**7, 1918.

3. Marinesco, C.: Contributions to the Study of the Pathological Histology of Encephalitis Lethargica, Reports to Local Government Board of Public Health and Medical Subjects, N. S., No. 121, p. 47, 1918.

4. Marie, P., and Trétiakoff, C.: Exam histologique des centres nerveux dans deux cas d'encephalite léthargique, Bull. et mém. Soc. med. d. hôp. d. Par. **42:**475, 1918; and Anatomie Pathologique de Z'Encephalite Léthargique, Ann. de méd. **7:**1, 1918.

5. Bassoe, P.: The Delirious and the Meningoradicular Types of Epidemic Encephalitis, J. A. M. A. **72:**971 (April 5) 1919.

6. Bassoe, Peter, and Hassin, George B.: A Contribution to the Histopathology of Epidemic (Lethargic) Encephalitis, Arch. Neurol. & Psychiat. **2:**24 (July) 1919.

7. Calhoun, H. A.: Histopathology of the Brain and Spinal Cord in a Case Presenting a Postinfluenzal Lethargic Encephalitis Syndrome, Arch. Neurol. & Psychiat. **3:**1 (Jan.) 1920.

8. Netter, A.: L'encéphalite léthargique épidémique, Bull. Acad. de Méd. Par. **79:**337, 1918.

Mott,[9] Flexner,[10] Smith in an article with Alexander and Allen,[11] and many others [12] are those of an acute inflammation which in its histology is not different in many of its characters from that which is known to occur in acute poliomyelitis or infantile paralysis.

Clinically lethargic encephalitis is an entity as distinct as that of acute poliomyelitis. It differs from this latter disease not only in its general clinical syndrome but also in its age incidence, its seasonal variations and in the course it runs.[13]

While this is true clinically, it is questionable whether any pathologic peculiarity of it has as yet been noted. The only one of any value which as been described so far is the distribution of the lesions. Whether this will hold in every case is an unsettled question. Infantile paralysis, as it is generally known, is a disease of the spinal cord. As Marinesco points out, Wickman has called attention to very constant alterations of the formation reticularis and the gray matter of the medulla and other authors have seen infiltration of the nuclei of the columns of Gall and Burdoch, of substantia nigra, of the gray matter surrounding the acqueduct of Sylvius, of the corpora quadrigemini and in the raphé and neighboring parts.

Lesions higher up in the brain have not been seen in acute poliomyelitis as far as the author is aware. In spite of this fact there are cases, however, which are classed with this disease and which show cerebral symptoms. Whether some of this latter type do not show lesions similar to those in encephalitis lethargica is a question yet to be answered and unless this is proven not to be true or one can find more characteristic lesions in the cases of lethargic encephalitis the pathological diagnosis between these two diseases must find its confirmation always in the clinical data. The etiological agent has not as yet been isolated.

Acute Poliomyelitis or Infantile Paralysis.—In 1919 I had the opportunity to study carefully at necropsy all the patients dying of infantile paralysis in Baltimore between August 28 and the end of the epidemic. The epidemic commenced later in that city than in many other parts of the east. More than fifty necropsies were performed, and excepting a very few at the beginning of the epidemic this included all the fatal cases of this disease in Baltimore that year.

9. Mott, L. W.: Discussion on Epidemic Encephalitis, Proc. Roy. Soc. Med., Lond., Med. Sect. **12**:1, 1918.

10. Flexner, S.: Lethargic Encephalitis, etc., J. A. M. A. **74**:865 (March 27) 1920.

11. Alexander, M. E., and Allen, H.: Lethargic Encephalitis, Arch. Neurol. & Psychiat. **3**:483 (April) 1920.

12. Stanton, J. M.: Epidemic Encephalitis: A Critical Review, Mod. Med. **2**:353, 1920.

13. James, S. P.: Discussion on Epidemic Encephalitis, Proc. Roy. Soc. Med., Lond., Med. Sect. **12**:9, 1918.

All the necropsies were complete. They were made on patients who died of respiratory failure in the acute stage of the disease. It was possible in these cases to study, therefore, not only the changes taking place in the central nervous system during the time the disease was active but also those peculiar to it in other organs and tissues of the body. The ages of these cases varied between a few months and 15 years. In more than 50 per cent. of the cases the cerebrum was congested, and in a few of the cases there was fluid in the subdural and the subarachnoid spaces of the meninges covering it. Unless other complications had arisen this fluid was clear and colorless, or slightly straw colored.

The more definite lesions were limited to the spinal cord, medulla, pons and the dentate nucleus of the cerebellum. No lesions were found in the midbrain or in any part above the upper end of the pons. In many of the fatal cases the disease as noted clinically made its first appearance low down in the lumbar cord and progressed upwards. It was of the so-called "ascending type." In other cases it was more focal.

The lesions in the cord were those of an acute inflammation. When the cases were treated as a whole the lesions were congestion, edema, hemorrhage, cellular infiltration, degeneration, necrosis, and proliferation.

Congestion and edema were the most constant alterations encountered. The edema was easily recognized in the gross by the tensely swollen cord, the substance of which on section of the meninges bulged forth to cover their cut edges. Although the amount of edematous swelling varied considerably in the different cases, it was usually present. Failure of the cord substance to push out through a broken point in the meninges of some part of the cord was seen in only two cases. This edema, together with the striking hyperplasia of the Peyer's patches, the solitary follicles of the ileum and colon, the mesenteric glands, especially those of the ileo-cecal region and the malpighian corpuscles of the spleen, gave a group of alteration which were found most useful in the gross diagnosis of the disease.

Histologically, it was of further interest to note that this congestion and edema, together with slight changes in the nerve cells, were often all that was found in the cervical region and medulla of persons who had undoubtedly died of respiratory failure. In one of the cases edema with hemorrhage made up the greater part of the lesions of the whole cord. This cord throughout was tensely swollen and peppered everywhere with tiny hemorrhages which gave it a striking appearance. The other changes noted in this case were a few cells in a few of the perivascular spaces of the vessels of the anterior horns

and a most constant hyperplasia of the endothelial cells lining the perivascular spaces about many of the larger veins, especially those which emerged into the anterior central fissure.

Hemorrhages were not present in all of the cases of this series. They were grossly noticeable in only a limited number and were proven microscopically to exist in only slightly more than fifty per cent. They were located in part in the tissue and in part in the perivascular spaces.

The most constant changes in the cords of these cases were, therefore, edema, hyperplasia of the perivascular endothelium—with or without perivascular infiltration, congestion of the blood vessels, diffuse and focal infiltration of the gray matter especially of the anterior horns of the cord and of the dorsal portions of the medulla and the tegmentum of the pons, various degrees of degeneration and proliferation and meningitis.

The cells which took part in what appeared to be a diffuse and focal infiltration of the tissue were of three kinds: Small mononuclear cells, which resembled lymphocytes or small polyblasts, larger mononuclear cells and polymorphonuclear leukocytes. These latter cells come without doubt directly from the blood stream. They were not seen in every case but only in those where the tissue had suffered necrosis. The sheaths of necrotic nerve cells contain often large numbers of them. Tiny abscesses were thus formed. In other areas often large masses of tissue had suffered a similar necrosis and invasion by these cells. These larger abscesses were found in the anterior horns of the cord, in the formatic reticularis and dorsal nuclei of the medulla, in the tegmentum of the pons and in the dentate nuclei of the cerebellum. The presence of these abscesses in this latter locality were of considerable interest because as far as the author is aware they have not been described previously in this locality.

Associated with the polymorphonuclear cells in the abscesses and scattered throughout the tissue there were also many of the smaller and the large types of mononuclear cells. In those cases where tissue necrosis is not marked and a less evident and slower degeneration of nerve cells is noted, these latter cells are the only ones present. It is in these cases that they can be seen definitely to be of two varieties. The large cells have a mass of granular but rather palely staining cytoplasm. The nucleus is small and rich in chromatin. They are either globoid or elongated in shape and very frequently processes can be seen extending from them into the tissue. These cells may occur isolated in the tissue or they may occur in groups. In the groups the central cells are generally globoid in shape while those in the periphery are elongated. These elongated cells have long processes

which connect them with the surrounding glia tissue. These cells the author considered were proliferated and degenerated glia cells and not cells which had entered this region from without. In this connection it is interesting that Buzzard and Greenfield [14] have noted cells like them in the brain of persons dead of lethargic encephalitis and these authors have also considered them of this origin. Holmes [15] ascribed the same origin to the large mononuclear cells of brain softening.

Associated with the accumulation of these cells in many of these cases there was also a more diffuse and evident proliferation of the glia tissue. This took place in part just outside the site of the greatest degeneration of tissue.

Many of the small mononuclear cells had a different appearance. They look more like lymphocytes. It was interesting, however, that all gradations between these small mononuclear cells and the larger type could be found. And, again, it was interesting to note that there were cases of rapidly progressing degeneration which showed few of these cellular changes.

The small cells were either diffusely scattered or collected in small clusters like those that look like glial cells. Many of the larger ones of this type look like polyblasts and few often resembled plasma cells. Their general appearance was such, however, that one was loath to class them in this group, but it was not definitely determined whether they had migrated like the polymorphonuclear leukocytes into this area or whether they had differentiated there.

The changes in the perivascular spaces were variable. The spaces more frequently involved were those about the veins draining the anterior horns of the cord, the formatio reticularis and dorsal portions of the medulla and the tegmentum of the pons. This was not always true, however, as Wickman has noted. In many cases many of the perivascular spaces about the arteries and all of the veins of both the white and gray matter were involved.

In the rapidly fatal cases showing little more than an intense edema, the spaces were generally greatly dilated and filled with pink staining granular material. There was slight hyperplasia of their endothelial lining cells and this membrane was frequently ruptured in places and the brain tissue compressed without. Such changes in these spaces were also seen in several instances in the cases of encephalitis lethargica reported above.

14. Buzzard, E.: Lethargic Encephalitis; Its Sequelae and Morbid Anatomy, Brain **42**:305, 1919.

15. Holmes, G.: The Pathology of Acute Spinal Injuries, Brit. Med. J. **2**:769 (Nov. 27) 1915.

In most of the cases of poliomyelitis as in lethargic encephalitis this dilatation was not so extreme, and the change consisted either of a striking hyperplasia of the endothelial lining cells or hyperplasia and a filling up of the space with small mononuclear cells.

As is well known the spaces about the larger blood vessels of the normal brain and cord are lined by a single or a double layer of flattened endothelial cells. These form a lining membrane which connects directly with the membrane lining the subarachnoid space of the meninges. The perivascular spaces about the small vessels and capillaries have no such endothelial lining. This system of perivascular spaces is what might be called the lymphatics of the central nervous system. The tissue fluid drains through them into the subarachnoid space from whence it gains entrance into the veins.

In poliomyelitis there were no changes in most of the spaces about the smaller blood vessels. The changes were limited largely to these spaces about the larger blood vessels which are endothelial lined. The lining cells were not like those of the normal brain but were greatly increased and had a definitely cuboidal shape. Their nuclei were spherical, vesicular and rich in chromatin. Many of these cells were seen to be desquamating or budding off into the subarachnoid space.

The cells that filled the space were small round cells which were apparently identical to these lining cells. Polymorphonuclear leukocytes were also seen in a number of these spaces. They were present only, however, in those cases where there were areas of tissue necrosis without which had been invaded by them. Besides these cells there were also a few larger clear mononuclear cells which had the appearance of swollen endothelial cells. There were also other cells which have been identified as polyblasts and plasma cells. All transitions between these various types and the endothelial lining cells could be found. The number of the cells in these spaces varied considerably. In many places the spaces contained very large numbers. The spaces were greatly distended. Their outer endothelial lining membrane had often ruptured in many places and the tissue without was edematous and the cells could be traced in numbers outwards from the space into the tissue. This was seen both in the gray and the white matter. It is possible that many of the small cells scattered in the tissue farther out may have been derived from this source. Many of them resembled these cells very much.

The meningeal changes were also variable. In the early part of the epidemic several of the cases were suffering from an acute purulent meningitis. This was seen, however, only in those cases which had been treated intraspinally with serum prepared from the blood of another patient who had recovered from the disease. This treatment

was soon discontinued in Baltimore. Subsequently no more cases with this form of meningeal change were encountered and it seemed evident, therefore, that it was not a part of acute disease, but that it had been a result of the serum treatment.

The simplest meningeal changes were congestion and edema. Microscopically, the spaces were dilated, the blood vessels were distended with blood and there was a small amount of pink staining granular material and a few small mononuclear cells scattered in the open space. In other cases the spaces contained larger numbers of small mononuclear cells and clusters of these cells were also seen in the walls of the larger blood vessels.

Active hyperplasia of the endothelial cells lining the subarachnoid space was not seen, except in a few of the cases, and when present it was often associated with hemorrhage. This fact became of interest because it was thought possible to associate it with the meningeal symptoms presented by a limited number of the cases. Unfortunately, however, the clinical data obtained for most of the cases was not sufficient.

The cell reaction in poliomyelitis is evidently, therefore, a mononuclear cell type. Peabody, Draper and Dochez [16] had already pointed out that polymorphonuclear leukocytes make their appearance only when there is active tissue necrosis. These authors considered the mononuclear cells to be lymphocytes from the blood stream. Marburg [17] had also the same view as to their origin. Wickman [18] calls them polyblasts in the sense of Maximow. Goldscheider [19] thought they were of glial origin while Strauss [20] considered them to be derived from the adventitial cells. Our studies would indicate that they were derived directly from the endothelium lining the perivascular spaces.

In this regard the recent work of Essick [21] becomes important. Essick noted endothelial hyperplasia and budding or desquamation in the subarachnoid space following the introduction of particulate matter into it.

16. Peabody, F. W.; Draper, C., and Dochez, A. R.: A Clinical Study of Acute Poliomyelitis, Monogr. Rockefeller Inst. M. Research, New York, No. 4, 1912.

17. Marburg, O.: (See Wickman, Ref. 18) 1909.

18. Wickman, I.: Acute Poliomyelitis (Heine-Medin's Disease), Nerv. & Ment. Dis. Monogr. S., No. 16, 1913.

19. Wickman: Loc. cit.

20. Wickman: Loc. cit.

21. Essick, C. R.: Formation of Macrophages by the Cells Lining the Subarachnoid Cavity in Response to the Stimulus of Particulate Matter, Contribution to Embryol. No. 42, Extr. f. Pub. 272, Carnegie Inst., Washington, p. 377, 1920.

The changes in the nerve cells in many of these cases of poliomyelitis consisted only of slightly evident degenerative changes. In a few cases the cells were swollen but they were generally slightly shrunken. Their nuclei stained palely and were shrunken. The cytoplasm was more densely granular. Mononuclear cells were often seen invading the space about these cells. These changes in other cases were more severe and proceeded to complete atrophy or to a rapid necrosis with fragmentation of their nerve fibers and an invasion of the space with polymorphonuclear cells as mentioned above.

Aside from these alterations, the sensory ganglion were also frequently involved in poliomyelitis. The changes were like those in the brain stem. They consisted of congestion, edema, hemorrhage and perivascular and diffuse infiltrations of small mononuclear cells. The changes in the ganglion cells varied from slight degenerative changes to complete atrophy or in other cases to necrosis with an invasion of polymorphonuclear leukocytes.

Evident involvement of the nerve fibers aside from secondary degeneration resulting from the destruction of their cells, was not observed in any of the cases. Further, neuritis has not been noted as far as the author is aware in any form in acute poliomyelitis by other authors.

The changes in the other organs in poliomyelitis were of two kinds: cloudy swelling of the heart, liver and kidney and a localized or generalized lymphoid hyperplasia. Focal necroses in the liver were not observed in any of our cases but it has been described by Peabody, Draper and Dochez.[16]

The lymphoid hyperplasia especially noted by these latter authors and mentioned above was most marked, however, in all of our cases. It reached its greatest intensity in the Peyer's patches and solitary follicles of the ileo-cecal region, the ileum, the colon and in the regional lymph glands of the mesentery and in the malpighian corpuscles of the spleen. In the cases of persons dying early in the disease the gross enlargement of the lymphoid tissue was largely limited to the spleen, the ileocecal region and the colon. In cases of slightly longer standing it became more general. All of the lymph glands and other lymphoid structures of the body, including the adenoids and tonsils, were enlarged and there were nests of lymph cells scattered in the wall of the bronchi and in other tissues and organs of the body.

The change in the lymph glands was not that of an ordinary infection but, on the other hand, it was that of a true hyperplasia. It differs decidedly from that seen in typhoid fever but may be found in many other conditions. Since this early study I have noted it in cases of

extensive skin burns, streptococcal infections with pronounced septi-
cemias, in diphtheria associated with degeneration of the nervous tissue,
in rabies, in tetanus and to a certain extent in acute cerebrospinal
meningitis and other infections of the meninges and in a number of
cases of brain tumors, especially gliomas.

The lymphoid tissue in the lymph glands in these hyperplasias is
greatly increased in amount. The blood vessels are congested. The
sinuses are generally collapsed and empty. The trabeculae are packed
with lymphoid cells. The follicles are striking. Their centers con-
tain a few or no lymphoid cells. They are filled with pink staining
granular necrotic looking material or a number of large granular
endothelial cells which contain no nucleus or one which is degenerating.
The peripheral part of the follicles contains large numbers of lymphoid
cells and at the sharply defined boundary between the periphery and
the center, mitotic figures are frequently seen.

The same changes are seen in the tonsils, the solitary follicles and
Peyer's patches of the intestines, and in the malpighian corpuscles of
the spleen. In the lungs and other organs simple densely packed
clusters of lymphoid cells are found.

Most of the cases of poliomyelitis occurred in otherwise healthy
children. A few, however, were complicated by an active tubercu-
losis and other diseases and a few also had developed a low grade
or an extensive bronchopneumonia associated with an acute enlarge-
ment of the spleen and more intense cloudy swelling of the organs.
The liver cells contain fat in a few of the cases. This was rarely
seen, however, and was associated generally with a chronic passive
congestion or some other complication.[22]

Lethargic Encephalitis.—Complete necropsies were obtained on two
of the cases of lethargic encephalitis reported above. In neither of
these cases was there any evident lymphoid hyperplasia. The absence
in the first case was not considered important. It was thought it might
have been influenced by the changes in the kidneys and in the blood
vessels which complicated this case. The second case, however, was
that of a young boy, aged 17. The lymphoid hyperplasia was most
marked in a case of poliomyelitis in a boy aged 15. It was absent
in this case which terminated fatally because of an acute lethargic
encephalitis of long standing.

In Case 1, there is marked degeneration of the nerve tissues in
the lower part of the thalamus. Active and intensive lesions are found
throughout the whole of the lower part of the thalamus, midbrain,
pons, medulla, the whole of the spinal cord and in several sections
of the cerebral cortex. They had reached, however, their greatest

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22. Taken from the unpublished notes of the author.

intensity in the lower part of the thalamus and midbrain or in the region of the substanția nigra, which has also been true of the large number of cases reported by previous authors. A similar distribution of lesions is seen in Case 2, while in Case 3, although the cord was not obtained, the lesions were apparently largely confined to the thalamus, internal capsule, parts of the lenticular nucleus, the midbrain and the pons. Marinesco described peculiar changes in the Purkinje cells of the cerebellum in these cases. Slight evidences of degeneration were seen in one section of Case 3, but these were absent in other sections.

In this same case (Case 3) there was also a diffuse and focal infiltration with beginning necrosis and a few polymorphonuclear cells in the substantia nigra. Marinesco, Buzzard and Greenfield and others have also noted these cells in these cases.

The myelin bodies noted in Case 1 were not seen in Cases 2 and 3. The disease in Case 1 had occurred in a middlle aged man. The brain lesion was complicated by a previously existing arteriosclerosis and atrophy. The myelin bodies were not different in their distribution and morphology from those seen in uncomplicated cases of cerebrospinal arteriosclerosis associated with atrophy of the brain substance and were, therefore, considered something apart from the acute disease.

The endothelial pearls seen in the meninges of the midbrain and about the trochlear nerve of Case 2 were more difficult to explain. Whether they were the result of previous changes in this part of the brain or a part of the existing, long standing acute illness could not be determined.

From this account it is evident, therefore, that the actual lesions in the central nervous system of lethargic encephalitis are not different histologically from a large number of cases of poliomyelitis. Buzzard and Greenfield in their recent careful description of a number of cases occurring in England have noted the same endothelial hyperplasia and the same type of cellular infiltration that I have noted in the cases of poliomyelitis. The changes in the nerve cells are also similar to those seen in the large number of cases of poliomyelitis.

The difference pathologically, therefore, between lethargic encephalitis and poliomyelitis is evidently not to be found in the minute histology of the nervous system but rather in the distribution of the lesions, the absence of marked edema and swelling of the spinal cord and the changes in other organs and tissues.

These systematic changes or changes in other organs, tissues and parts of the body we give with reserve because we have been able to study more or less completely only two cases of this disease. Whether

a general lymphoid hyperplasia may not occur in a limited number of these cases is of course something which the future alone can decide.

The neuritis of the cranial nerves, on the other hand, form apparently a more distinctive difference. Again, its discovery is interesting because neuritis of the cranial nerves is a rare condition. It was marked in Cases 1 and 2 and present in the optic nerve and in a few of the other cranial nerves in Case 3.

McNaulty [23] in classifying clinically the cases of lethargic encephalitis [24] as they occurred in England previous to the writing of his article noted six groups. They are as follows:

Group I. Cases with general symptoms and without localizing signs.

Group II. Cases with third nerve paralysis and general disturbances in the function of the central nervous system.

Group III. Cases with facial paralysis and general disturbances in the function of the central nervous system.

Group IV. Cases with spinal manifestations and general disturbances in the function of the central nervous system.

Group V. Cases with polyneuritic manifestations and general disturbances in the function of the central nervous system.

Group VI. Cases with mild or transient manifestations (so-called "abortive" cases).

Throughout the epidemic of lethargic encephalitis which has raged in this country and Europe cases of polyneuritis have been continually reported and have been associated clinically with those cases showing cerebral symptoms. It has been of interest therefore to report these three cases here and the neuritis noted in their cranial nerves not only because of the bearing this finding has in distinguishing this disease from acute poliomyelitis but further because it gives a definite pathologic basis of union of these various types with those of true lethargic encephalitis.

Cases 1 and 3 of this series belong to McNaulty's Group II while Case 2 falls quite clearly among those cases which he places in Group V.

23. MacNaulty, A. S.: A Clinical Account of the Disease and the Opinion as to Its Nature Which Seems Justifiable from Clinical Inquiry. Reports to Local Government Board on Public Health and Medical Subjects. Report of an Inquiry Into an Obscure Disease, Encephalitis Lethargica, N. S., No. 121, p. 12, 1918.

24. The name "encephalitis lethargica" is evidently not a good one for this disease when it is considered in its broader aspects. "Epidemic encephalitis" is undoubtedly preferable. I have used the name lethargic encephalitis in this paper for another reason and that is to emphasize the fact that a definite neuritis may occur in cases showing largely cerebral symptoms and lethargy as a prominent one.

BOOK REVIEWS

THE PATHOLOGY OF INFLUENZA. By M. C. WINTERNITZ, ISABEL M. WASON, and FRANK P. McNAMARA. Yale University Press. 1920.

This is a well illustrated description and summary of the morbid changes largely mentioned in the current literature on influenza. Much of the text is devoted to the gross and minute pathology of the respiratory tract both in the acute and in the subacute or chronic stages, incidental lesions in other parts of the body being presented briefly.

In a group of ninety-five patients there were two with activation of a chronic pulmonary tuberculosis by influenza.

The bacteriology of influenza is reviewed broadly. All the reports mention more or less constantly the pneumococcus group, streptococci and the Pfeiffer bacillus, occurring alone, together, or with other less frequently found organisms.

There is a comparison between the respiratory lesions in influenza and those initiated experimentally in animals by the inhalation of poisonous gases. Although an interesting similarity is noted, the changes have been observed in experimental animals rather than in human beings, which precludes making definite conclusions.

The authors say the etiology of influenza is unknown, the portal of entry is undetermined, and the respiratory lesions, whether primary or secondary, are responsible for the high mortality of the disease.

This study thoroughly summarizes our present knowledge of the pathology of influenza.

A DIABETIC MANUAL FOR THE MUTUAL USE OF DOCTOR AND PATIENT. By ELLIOTT P. JOSLIN, M.D., Assistant Professor of Medicine, Harvard Medical School. Second edition. Cloth. Price, $1.75. Pp. 191 with illustrations. Philadelphia: Lea & Febiger, 1919.

The 1919 edition of Dr. E. P. Joslin's Diabetic Manual, like the 1918 edition, has been written with the knowledge and needs of the patient especially in mind. There is probably no disease, the successful management of which depends so largely on the intelligent cooperation of the patient. Occasionally, a fatal case is found where the physician feels that the patient knows too much about his case, but we agree with the author when he states in his introduction: "I still feel that for one diabetic patient who learns too much about the disease, there are unquestionably ninety-nine who know too little. Those of my patients who are the most intelligent and who understand the disease the best live the longest."

The chapters are short and easy to read. The statistics given in the opening chapters show such a marked improvement in the course of the disease that the patient obtains a hopeful rather than a depressing outlook. This edition is simpler than the first. Additional test diets have been added. Added information is given about blood sugar and the importance of low caloric diets. The dangers of diabetes are described so that the patient will help the physician to prevent gangrene and acidosis. The index has been improved.

Physicians desiring to learn the newer methods of the treatment of diabetes should read this book before reading larger volumes.

HYPERSENSITIVENESS TO ARSPHENAMIN FOLLOWING EXFOLIATIVE DERMATITIS *

A CUTANEOUS TEST

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AND

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Following the use of arsphenamin or neo-arsphenamin in the treatment of syphilis, a variety of untoward reactions are frequently noted, some of which are well known to all who use this form of therapy and of very temporary moment; others, fortunately less frequent, are of far more serious consequence. These manifestations are sufficiently distinct in time of occurrence, nature and duration to have received special names, but all the types are easily confused and very frequently no attempt is made to differentiate them. It seems important, however, to do so, because very serious consequences may occasionally be avoided by an early recognition of signs which indicate the onset of one of the more serious types.

The most serviceable classification of these phenomena to be found in the recent literature is that of Sicard and Roger.[1] We have adopted this classification with certain modifications and our review of published cases, as well as observation of patients treated at the Presbyterian Hospital, has shown it to be simple and adequate. We recognize four types, with subdivisions of the third, dependent on the organ most manifestly injured:

1. Nitritoid crisis.
2. Herxheimer reaction.
3. Acute arsenic poisoning: (*a*) renal type; (*b*) hepatic type.
4. Chronic arsenic poisoning.

To this list might be added cases of simple overdosage or improper preparation of the drug, but as modern methods and knowledge have almost eliminated this group, we will not consider them here as responses to arsphenamin treatment. The four groups mentioned occur despite the most careful dosage and technic of administration.

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* From the Medical Clinic of the Presbyterian Hospital.

1. Sicard, J. A., and Roger, H.: Bull. et mem. Soc. méd. d. hôp. de Par. **13**:181, 1918.

It should be emphasized that, except for the nitritoid crises,[2] all of these reactions are of exceedingly infrequent occurrence, although we have no statistics of their relative incidence in a large series of cases.

The limits of this paper do not permit a detailed consideration of the first three types. The chronic arsenic poisoning cases are those in which we are especially interested because they are so severe in their manifestations and yet so insidious in onset, that we believe they may be avoided by due care in watching for early symptoms and by an adequate knowledge of the difference between these and the symptoms of the other types. We propose to present our case at this time and in the discussion to point out the characteristics of this form of poisoning.

REPORT OF CASE

History.—Mrs. G. L., aged 43 years, was admitted to the Presbyterian Hospital May 16, 1919, for antisyphilitic treatment on learning that her husband was a syphilitic, suffering from general paresis. Eight years before she had had a sudden paralysis of the left arm and leg and the right side of the face with some involvement of speech. This condition completely cleared up in one year.

Physical Examination.—The general physical and neurologic examination on admission showed Argyll Robertson pupils, atrophy of the muscles of the left leg and thigh, unequal knee jerks, the left greater than the right, a left exhaustible ankle clonus, left patellar clonus, left Babinski and confirmatory reflexes.

Laboratory Examination.—The blood Wassermann was: alcoholic antigen +++, cholesterin antigen ++. The spinal fluid Wassermann was: alcoholic antigen, +++ in 0.2 c.c.; cholesterin antigen, +++ in 0.6 c.c. The colloidal gold curve was: 5555544210. There were 91 cells per cm. in the spinal fluid, 91 per cent. lymphocytes and 9 per cent. polymorphonuclears. Globulin, ++.

Treatment.—On the basis of the laboratory data, antisyphilitic treatment was begun at once. Mercury bichlorid, 1 grain, was given intramuscularly at intervals of a week for three doses, and at the same time potassium iodid, in three courses, to a total of 2,365 grains by mouth was given. After the second mercury injection, intravenous arsphenamin was begun. The patient received six intravenous treatments, one a week, the dosage being 0.2, 0.3, 0.4, 0.4, 0.4, 0.4 gm., respectively. There was no reaction of any kind following these intravenous treatments.

The fourth intravenous treatment was combined with an intraspinous injection, using the Swift-Ellis technic without reinforcing the serum. This caused some pain and soreness in the lumbar region, radiating down the legs. The sixth intravenous treatment was also combined with an intraspinous injection and was followed by the same pain in the lumbar region and legs. This time, however, the pain grew worse until walking became very difficult. The urine was definitely bloody on two occasions.

The patient was readmitted five days after the treatment with very definite signs of meningeal irritation; a stiff neck, double Kernig and fever. The spinal fluid showed an increase in pressure and was sterile. A bloody tap made cell count and globulin estimation impossible. A blood culture was sterile and there was no leukocytosis. The urine showed only a very faint trace of albumin and no red blood cells or casts. The temperature gradually reached normal in

2. Berman, L.: Arch. Int. Med. **22:**217 (Aug.) 1918.

Neoarsphenamin
1:1,000.

Arsphenamin
1:1000.

1:5000.

1:5000.

1:25,000.

1:25,000.

1:125,000.

The cutaneous reactions seventy-two hours after injection of arsphenamin and neo-arsphenamin in varying dilutions.

one week and the signs of meningeal irritation slowly cleared up. The picture was thought to be that of a sterile leptomeningitis due to the introduction of serum into the spinal canal.

Twelve days after admission, the patient was given her seventh dose of arsphenamin, 0.4 gm. This was immediately followed by severe sharp pain over the sacrum and down the legs which disappeared during the night. There was also some erythema on the back of the left wrist and urticarial spots on the left deltoid. The next day she had a fine, itching, erythematous rash on the wrists and shins which was relieved by epinephrin. This lasted two days and was considered to be an urticarial phenomenon, part of a mild nitritoid crisis.

One week later another 0.4 gm. of arsphenamin was given, making eight doses in nine weeks and three days. The treatment was followed in one hour by vomiting and transitory headache. The next morning there was definite swelling of the hands, forearm and feet, most marked in the left hand with slight redness and severe itching. The urine showed only a very faint trace of albumin and no red cells or casts.

Second Admission.—The patient was discharged but returned four days later because the swelling had rapidly progressed until it involved all the extremities, the chest, face and neck. There had been slight nausea and weakness, and the urine output had noticeably decreased.

Physical Findings.—On admission, the temperature was 98.8 F., pulse 84, and respirations 20. The face was swollen and of homogeneous dull red color without cyanosis. The eyelids, particularly the upper, were puffy, and there was slight conjunctival congestion and lacrimation. The nose showed a mild coryza, but the mucous membranes of the mouth showed no changes. Over the arms and legs was a diffuse erythema made up of small red areas, nearly confluent. The skin was dry, warm and rough, with a fine, branny desquamation. Pressure caused pain. The erythema extended to a lesser degree over the entire trunk, including the abdomen, being most marked in the dependent portions of the body. There was marked swelling of the hands, forearms, arms and legs, with a peculiar induration and pitting edema. .There was some edema beneath the skin of the neck, anterior chest and back. The lower extremities presented marked vasomotor paresis, becoming a deep red when they hung in a dependent position.

Laboratory Findings.—There was a marked polymorphonuclear leukocytosis. The leukocytes numbered 20,000; polymorphonuclears, 87 per cent., of which 35 per cent. were eosinophil. The phthalein excretion was 39 per cent. in two hours. Blood pressure, 104/80. Urine: sp. gr., 1.014; albumin, negative. Sugar: negative; no casts or erythrocytes. Chlorids, 4.4 gm. per liter.

Clinical Course.—The patient was in the hospital two months and seven days. The skin manifestations dominated the picture. The erythema became a homogeneous dull red, edema was marked and the desquamation became generalized, the dead epithelium pulling off in large flakes The skin showed a tendency to fissure wherever natural folds occurred, but very few denuded areas appeared. Profuse, sour smelling perspiration was a disagreeable feature. There was marked falling of the hair and the finger and toenails were in process of desquamation on discharge. Some erythema and skin exfoliation persisted and recurred in small areas even four months after the onset of the illness.

Bronchopneumonia was a serious complication. This occurred in the second week and subsided in four days. Perhaps the most alarming feature of the illness, however, was an acute nephritis that developed in the third week and did not begin to clear up until the sixth.

There was a marked obliguria, 190-550 c.c. of urine in twenty-four hours on a fluid intake of from 1,600 to 3,000 c.c. The blood urea was 0.44 gm. per liter, and the plasma carbon dioxid, 57.6 volume per cent. Urinalysis showed from a very faint trace to a trace of albumin with many hyalin casts. A phenolsulphone

Fig. 1.—The dermatitis at its height in the second week.

phthalein test was unreadable in one hour, because of discoloration of the urine and 10 per cent. at the end of two hours. The chlorid output was 2.7 gm. per liter. In the sixth week, the urine output rose to from 1,000 to 1,900 c.c.; no more casts were seen and the blood urea dropped to 0.21 gm. per liter.

The leukocyte count was very interesting in that there was a very marked eosinophilia during the height of the dermatitis. On one occasion, the white cells numbered 20,000, with 87 per cent. polymorphonuclear leukocytes, of which 35 per cent. were eosinophils. The leukocytosis and eosinophilia gradually diminished until during convalescence the count was: leukocytes, 8,500; polymorphonuclears, 61 per cent., with 1 per cent. eosinophils.

Other complications of the arsenic poisoning were a purulent conjunctivitis and deafness due to occlusion of the external auditory canal by desquamated epithelium. Peculiar trembling, chilly sensations were annoying and seemed to have no relation to adequate body warmth. They were relieved by baking. *B. pyocyaneus* was recovered from urine cultures and from axillary and pectoral abscesses that developed during the illness. The gastro-intestinal symptoms described in arsenic poisoning, i. e., nausea, vomiting and diarrhea, were never manifest.

Arsenic was found in the urine, by means of a modification of the Marsh test and persisted throughout the course, being present ninety-seven days after the last dose of arsphenamin.

Subsequent Course.—The patient has been seen four times since discharge, Oct. 21, Oct. 31, Nov. 28, 1919, and Feb. 1, 1920. Twenty-four days after discharge she complained of a slight transitory rash coming out first on the neck and arms. This appeared as tiny, red, itching elevations that became scaly and then disappeared. The skin everywhere was a little redder than normal and thickened in the folds. Seven weeks after discharge, she was still troubled with the occasional appearance of this rash. Otherwise she felt very well and weighed more than she had in twenty-three years.

Treatment.—The treatment was aimed at elimination of the arsphenamin and consisted in forcing fluids, colon irrigations and mild catharsis. Cold cream and boric acid ointment were used for the dermatitis.

DISCUSSION

It is of interest to note that this case of exfoliative dermatitis developed after the seventh dose of arsphenamin. The dosage had certainly not been excessive as it had never exceeded 0.4 gm., and the total amount was 2.5 gm. at the time the first rash appeared. The poisoning can be explained on the supposition that the patient belongs to that group of individuals that show a hypersensitiveness to arsenic or that there was an accumulation of arsenic in the tissues due to faulty elimination. There is some evidence for the second of these theories. First, the patient gave a history of bloody urine at the onset of the meningitis and an acute nephritis developed subsequently. Second, arsenic was present in the urine throughout the illness. It seems likely that the kidneys were primarily at fault. During the course of arsphenamin, they failed to eliminate the requisite amount of arsenic between treatments and the gradual accumulation of the drug resulted in an arsenical dermatitis and an acute nephritis.

·The earliest signs of sensitiveness to arsenic are also extremely important. The irritative meningitis and hematuria that followed the sixth treatment may have been the first expression of this. At least,

it is fair to say that the serum produced a degree of irritation far beyond that usually seen after the Swift-Ellis treatment. The first manifestations in the skin came after the seventh dose of arsphenamin, when there immediately appeared some erythema on the back of the left wrist and urticarial spots on the left deltoid. The next morning there were very fine, itching, fairly discrete macules and papules on the wrists and shins, very probably a true arsenical dermatitis. Therefore any eruption occurring after the taking of arsphenamin, except the sudden blotchy urticarias that accompany a nitroid crisis, should be construed as an indication of sensitiveness to arsenic and a prolonged rest from treatment by arsphenamin should be given. If in addition to the rash, there is edema of the extremities with diffuse redness and itching, an arsenical dermatitis has already begun and all treatment by arsenic must abandoned for a time at least.[2a]

Cases of exfoliative dermatitis coming on after the intravenous use of arsenical preparations have been reported by Carr,[3] Malherbe,[4] Sicard and Roger,[1] Latham,[5] Evans,[6] Moore and Foley,[7] Didry[8] and Bine.[9] Mook,[10] while studying skin reactions to apothesin and quinin, tried to obtain a reaction to arsphenamin in a hypersensitive person by rubbing a solution of arsphenamin into a small scratch in the skin. This test was negative and constitutes the only recorded attempt to demonstrate hypersensitiveness by a cutaneous test. Sensitiveness to sodium cacodylate after one or more subcutaneous injections has been reported by Kauffmann[11] and Stäuble.[12] At the suggestion of Dr. W. T. Longcope, we have studied the local reaction excited by intradermal injections of varying dilutions of arsphenamin, neo-arsphenamin and other control substances in a series of twenty-six cases, in an attempt to find some means of foretelling which cases are hypersensitive to this preparation of arsenic, and, therefore, of possibly preventing such disastrous reactions. We were able to carry out these tests on the case reported above over eight months after the onset of the dermatitis, and we believe our results are of sufficient interest to warrant presentation at this time.

2a. Since the above was written French (Lancet **1**:1262, 1290) has reported several cases of exfoliative dermatitis in which he has resumed treatment cautiously with good results.

3. Carr, E. B.: Proc. Med. Ass'n C. Z. **10**:115, 1917.

4. Malherbe, H. (des Nantes): Ann. d. mal. ven. **12**:662, 1917.

5. Latham, J. R.: J. A. M. A. **73**:14 (July 5) 1919.

6. Evans, F. A.: Arch. Int. Med. **17**:1 (Jan.) 1916.

7. Moore, J. E., and Foley, F. E. B.: Arch. Dermat. & Syph. **1**:25 (Jan.) 1920.

8. Didry: Ann. d. mal. ven. **11**:723, 1916.

9. Bine, R.: Boston M. & S. J. **175**:96, 1916.

10. Mook, W. H.: Arch. Dermat. & Syph. **1**:651 (June) 1920.

11. Kaufmann: Deutsch. med. Wchnschr. **39**:272, 1913.

12. Stäuble: Deutsch. med. Wchnschr. **38**:242-245, 1912.

OUTLINE OF TESTS AND METHODS

The arsphenamin and neo-arsphenamin used in all tests were obtained from freshly prepared solutions about to be used in therapy, and corresponded exactly in sterility, neutrality and freshness to that used intravenously. These supplies were always made up in dilution of 0.1 gm. to 20 c.c. and further dilutions were made in sterile distilled water to give final dilutions of 1 : 1,000, 1 : 5,000, 1 : 25,000, 1 : 125,000, respectively. Dilutions of 1 : 200 were tried in the first few cases, but this concentration always produced a local irritation so that in subsequent tests it was not used. This irritation was occasionally met with after the injection of dilutions of 1 : 1,000, but the evidences of irritation were so delayed in appearance that they could not be confused with the reaction noted. A firm elevated nodule appeared in the skin at the site of injection after an interval of several days and increased in size and intensity until about the tenth to fourteenth day, then gradually disappeared after many weeks. These nodules would itch and occasionally show central necrosis.

As controls fifthieth-normal sodium hydroxid solution having an alkalinity greater than that of the arsphenamin, was used in most cases, but simple distilled water or physiologic sodium chlorid solution were used in a few. Others were also tested with sodium cacodylate as an arsenic containing control.

The technic of administration was to introduce into the superficial layers of the dermis sufficient solution to create a swelling from 3 to 4 mm. in diameter. The forearm was sterilized with alcohol and a sterile tuberculin syringe was employed. The various substances were thus introduced 3 inches apart along the volar aspect of the forearm and a chart of their distribution was kept for recording purposes. An attempt was made to make observations one-half hour, six hours, twenty-four hours and forty-eight hours after injection, and if any reaction appeared this was observed on subsequent days. This schedule could not be followed in detail in all cases tested, as some were dispensary patients; but in no case was the reaction called negative unless observations had been made for at least forty-eight hours after injection. Furthermore, many of the controls were performed on members of the house staff, who could be followed closely and who were able to supplement our readings by frequent examinations themselves.

The twenty-six cases which have been examined by this method can be divided into four groups:

1. Syphilitics treated with arsphenamin, developing severe exfoliative dermatitis; three cases.

2. Syphilitics treated with arsphenamin and having had no reaction or only immediate and temporary nitritoid reactions; seven cases.

3. Syphilitics having never received arsphenamin; six cases.

4. Nonsyphilitics and untreated controls; ten cases.

In the greater number of these cases, there was an immediate blotch of erythema surrounding the injection, just as constant in the control as in the test injections and fading within a few minutes or hours. There was also a minute papule or macule at the sight of inoculation, which would persist sometimes two or three days. This was usually a little more marked about the sodium hydroxid injection than about the other injections. The more marked reactions met with about the stronger dilutions of arsphenamin have been mentioned. All these were considered normal responses to local irritation and only cases showing these reactions were considered to be negative.

On this basis our results showed that all cases falling into groups two, three and four, that is twenty-three controls, were negative. In the first group we placed the case reported above, a case referred to the Presbyterian Hospital by Dr. J. A. Fordyce three months after a moderately severe exfoliative dermatitis, occurring during a first course of arsphenamin therapy, and a third referred from the Vanderbilt Clinic nine months after a generalized exfoliative dermatitis. The latter patient had suffered from a scaly eruption of the scalp and to a less extent of the body for many years before treatment had been begun. He had received course after course of arsphenamin over a period of years, and was away on a vacation without having received any of the latter drug for over a month when his extensive dermatitis appeared. It was, however, the concensus of opinion at the Vanderbilt Clinic, that this was a true arsphenamin dermatitis.

In the first two cases, we obtained very definite and quite similar reactions, varying only slightly in intensity. We had an opportunity of repeating the tests and following more closely the case reported herewith, and, therefore, we shall describe the reactions which followed these injections.

The patient was tested at five months and again at eight months after the onset of her dermatitis, and both times she showed a very unusual local reaction. It did not, in any particular, simulate the urticarial phenomena met with following the injection of foreign proteins, nor did it appear like the local necrosis produced even in controls by too concentrated solutions of arsphenamin. From six to eighteen hours after the injections, there appeared about the dilutions of 1 : 1,000, of both arsphenamin and neo-arsphenamin, a central elevated and finely indurated nodule about the size of a dime, dark red in color and itching intensely, surrounded by an outer zone three inches in diameter, rather whitish near the center, but quite red toward the

periphery. This outer margin was irregular, very slightly elevated and appeared even at this stage to be composed of minute papules united by an erythema, giving the appearance of goose flesh. Similar patches, diminishing in size, appeared about the greater dilutions down to the dilution of 1:125,000, which showed only a very small patch, not larger than the original injection.

At twenty-four hours, all the patches had become redder, and at forty-eight hours, the "goose-flesh" nature of the surface had become more pronounced and the distinction between inner and outer zones was less marked. At this time there was slight moisture over the strongest dilutions, but at all other times the reactions were dry. By the third day, all had diminished somewhat in size and showed quite rough surfaces and the edges were more irregular and formed by small discrete and firm papules.

On the fourth day after the intradermal tests, the patient felt nauseated and had severe pain in the lumbar region similar to that experienced after the intraspinous treatments. These persisted for about four weeks and then disappeared. There were no vomiting, lancinating pains or urinary disturbances and it seems hardly probable that the minute amount of arsenic injected could account for the disturbance. The skin reactions remained about as described for eleven days and then rapidly subsided.

Five weeks after the tests were performed, there were faint pink scaling spots at the sites of the injections of neo-arsphenamin in dilutions of from 1:1,000 to 1:25,000, likewise small red papules, diminishing in size from the same dilutions of arsphenamin. Itching was the only subjective symptom throughout. No reaction appeared at any time about controls of sodium hydroxid or sodium cacodylate. The second patient was tested three months after her dermatitis. The reaction was first noted at twenty-one hours and the patches never became as large, but the process had similar characteristics. They were still present when the case was last seen one week after the injection, the color having become a little browner and the surface showing a few fine scales. No reaction was noted about the controls of sodium cacodylate or physiologic sodium chlorid solution. The dilutions of neoarsphenamin were not used in testing this case.

The third case showed absolutely no reaction to either the arsphenamin or neo-arsphenamin test solutions or to the controls during the nine days over which he was followed.

The reaction met with in the first two cases seemed to be entirely too definite to be interpreted as anything less than a hypersensitiveness to some constituent of the arsphenamin preparation, present for from three to eight months after an extensive exfoliative dermatitis. This

hypersensitiveness was not found in a third case nine months after the dermatitis. We are unable to explain this, except on the ground that the hypersensitiveness, developed during the courses of therapy, had worn off during the nine months of freedom from treatment in the last case. It may be that this patient could now tolerate further arsphenamin therapy, but more cases are necessary to establish the value of intradermal tests as a guide for therapy.

These considerations make it evident that more tests will have to be performed on cases that have recovered from an arsenical dermatitis at varying intervals after their exfoliation, before the reactions will become of any practical value; but we believe that the results thus far obtained show that intradermal injections of dilutions of arsphenamin may be an index of a latent susceptibility. The only object in reporting these findings before more definite conclusions have been drawn from them is that thereby the series of tested cases may be increased. It is a rare condition, and our contact with it has been very limited; but we are very anxious that as cases appear from time to time they shall be tested in the very simple manner outlined above.

SUMMARY

I. Reactions following arsphenamin or neo-arsphenamin therapy may be divided into four types:

1. Nitritoid crisis.
2. Herxheimer reaction.
3. Acute arsenic poisoning
4. Chronic arsenic poisoning.

II. A case of exfoliative dermatitis or chronic arsenic poisoning is presented. The first cutaneous manifestations were persistent itching, papular eruptions on wrists and shins. It is possible that the irritative meningitis following the preceding treatment may have been the beginning of the symptoms of hypersensitiveness.

III. Cutaneous hypersensitiveness to arsphenamin and neo-arsphenamin occurs in patients who have suffered from exfoliative dermatitis. This was demonstrated by typical skin reactions in two such patients by means of intradermal injections of minute dilutions of the drug, but could not be demonstrated in a third, perhaps because the tests were made nine months after the dermatitis when the hypersensitiveness had subsided. This supposition, if substantiated, would make the skin reaction of practical importance in determining when it is safe to renew arsphenamin treatment.

EPIDEMIC INFECTIOUS JAUNDICE AND ITS RELA-
TION TO THE THERAPY OF SYPHILIS *

JOHN H. STOKES, M.D., and RUDOLPH RUEDEMANN, Jr., M.D.

WITH AN INTERPRETATION OF THE DUODENAL FINDINGS BY

WILLIS S. LEMON, M.D.

ROCHESTER, MINN.

The present study of icterus which develops during antisyphilitic treatment was inspired by the following circumstance: A patient who had completed twelve injections of arsphenamin at our hands in September, 1917, returned for observation in July, 1918, with a history of having been severely jaundiced in May, about nine months after his last arsphenamin injection. He volunteered the statement that his jaundice had been associated with a severe attack of multiple arthritis which came on following a cold, and that his brother had had an even more severe attack of arthritis with jaundice at the same time. The brother had never had syphilis and had never been treated for it. Circumstances in other cases suggesting an acute infection and sporadic cases of catarrhal jaundice which have also come under our observation (one occurred in a member of our staff), have further aroused our interest.

Moreover, in the recent American and European literature reports and discussions have appeared of the apparently frequent occurrence of occasionally fatal jaundice, ascribed by the authors to syphilis or the administration of arsphenamin. We have, therefore, felt it worth while to analyze and record our experience with this complication. The analysis of our material presents, we believe, strong circumstantial evidence to the effect that while antisyphilitic treatment may have a predisposing influence, such therapy may have been of minor importance during the past two years. The major or exciting cause may be an infection of as yet unknown etiology, possibly a tardy manifestation of epidemic influenza.

From August, 1916, when the Section on Dermatology and Syphilis of the Mayo Clinic was organized, to July, 1920, seventy cases of jaundice have come under our observation excluding those definitely associated with carcinoma of the liver. During this period the department has had under observation approximately 5,200 patients with syphilis. A certain percentage of these patients have passed from observation since this study was begun so that it was necessary to

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* Studies from the Mayo Clinic.

communicate with the patients by questionnaires.   Inquiries were also sent to physicians under whose care certain of these patients had been during their absence from the Clinic.   The incidence of jaundice in our cases from all causes, therefore, does not exceed 1.3 per cent. The proportions represented by these figures should be borne in mind in any attempt to compare our experience with that of others.

One of us (Stokes), speaking from the experience of the past seven years, can confidently say that jaundice is a relatively rare incident in the types of syphilis and the forms of antisyphilitic treatment with which he has been concerned.   In particular, jaundice has been an exceedingly rare complication of the first two years' experience of the Section on Dermatology and Syphilology.   Not more than six cases were observed during this period (1916-1918).   The methods of treatment employed during the first two years (August, 1916, to August, 1918) differed in no important respect from the methods used during the last two years (August, 1918, to July, 1920).   Accordingly, the abrupt occurrence of sixty-four cases of jaundice between August, 1918, and July, 1920, certainly suggests the operation of some factor other than arsphenamin or antispecific treatment in the abstract to account for so singular a distribution.   Meirowsky's statistics, prepared for the Allegemeiner Aertzlicher Verein of Cologne, based on 225,780 injections of arsphenamin, neo-arsphenamin, and arsphenamin sodium show the complication to be rare.   In this unprecedented series jaundice occurs once in each 2,000 injections of arsphenamin (0.89 per cent.) and once in 6,000 injections of neo-arsphenamin.   This estimate exceeds that of our experience.   Even on the basis of the Meirowsky figures the expectancy for the incidence of postarsphenamin jaundice on this service up to June, 1920, would not exceed fourteen cases (28,000 injections).   Since the method of administration of arsphenamin has remained constant, or, if anything, has been definitely improved as our experience enlarged, there remains a margin of fifty-six cases of jaundice to be explained by other causes than treatment *per se*.

Special toxicity of the drug employed must be considered.   We have used the Dermatological Research Laboratory brands of arsphenamin and neo-arsphenamin practically continuously for three years. The high reputation of these products and the fact that no other manifestation of a heightened toxicity of the drug has been associated with the jaundice throughout so long a period of observation seems to exonerate the drug.   Considerable concrete evidence at least will be needed to show that the increased incidence of jaundice during the period from November, 1919, to March, 1920, is a function of the toxicity of this brand of arsphenamin during this particular period of its manufacture.

The Clinical Picture of the Group Before Jaundice Appeared.—
The seventy patients who developed jaundice in the period from
August, 1916, to June, 1920, included examples of every aspect of
syphilis, and, in addition, four patients in whom it could be excluded
with reasonable certainty. Two of these patients had tuberculous
glands, one had actinomycosis of the cecum, and one had indefinite
symptoms for which he received a therapeutic test with negative results.
Fifty-six per cent. of patients had neurosyphilis and 18.5 per cent.
had latent syphilis with positive Wassermann reactions. Duration of
infection ranged from four months to twenty-six years, more than
half being in the second decade of their infection. Ages ranged
from 8 to 59 years. The matter of hepatic involvement is important
because of its bearing on the cause of the jaundice. Only 9 per cent.
of the patients had palpable livers, and 4 per cent. had palpable spleens.
Abdominal tenderness on first examination was present in 16 per cent.,
about equally divided between the upper and the lower abdomen. In
investigating for surgical causes of jaundice, it was found that only
three patients gave a previous history of icterus, and one was jaundiced
from hepatic cirrhosis at the time of entry. One patient had a medical
diagnosis of probable cholecystitis before jaundice appeared, and one
was operated on in 1910 and gallstones were found. The condition
of three patients which was clinically diagnosed cholecystitis cleared
up under arsphenamin treatment. The gallbladder of one of two
patients operated on during the attack was found to be negative, the
other had cholecystitis with fine adhesions around the gallbladder and
enlarged regional lymph nodes. Seven had sustained appendectomies
and one had symptoms suspicious of appenditicis. In all only 23
per cent. of our cases presented anything even suggestive of abdominal
nonsyphilitic pathology, and in only 13 per cent. did the signs point
toward the liver and the biliary tract.

Laboratory findings on first examination showed 61 per cent. of
the patients to have weakly or strongly positive Wassermann reactions.
The percentage was reduced one half by the treatment they received.
The incidence of jaundice had no appreciable effect on the percentage
of positive reactions after the patients had recovered.

Sixteen per cent. of the patients had abnormal urines, the degree
of abnormality being usually slight. The large majority had normal
blood findings.

Study of accessible foci of infection in fifty-eight patients showed
that about two thirds had moderately septic teeth or tonsils, and foci
in the genito-urinary tract were at times present, but no distinct rela-
tion between these findings and the incidence of jaundice seemed
demonstrable. Five patients whose dental and tonsillar foci had been
removed nevertheless developed jaundice.

Prodromal Period.—Data on time relations from forty-seven cases show the prodromal period in 65 per cent. to be two weeks or less. Seven patients had prodromal periods of three weeks, and five had thirty days.

Of special interest in the consideration of an etiologic infection was the frequency of coryza, tonsillitis and pharyngitis, influenza and grippe as a feature of the prodromal period. Forty-one per cent. of fifty-eight patients of whom data were obtained developed such manifestations before or in association with their jaundice. One patient had pneumonia with jaundice, and another had a sequence of coryza, bronchitis, influenza, jaundice, and bilateral otitis media, with recovery. The symptomatology of the prodromal period based on fifty-two cases is given in Table 1.

TABLE 1.—Symptomatology

	Percentage of Patients
Lassitude and prostration	77
Loss of weight (up to 9 pounds)	45
Coryza, tonsillitis, pharyngitis, influenza, etc.	41
Pains in joints and muscles	40
Nausea and vomiting	32
Constipation	20
Anorexia	19
Diarrhea	13
Cutaneous manifestations (purpura, erythema)	4

Aching pains and stiffness in the back, shoulders and legs were much complained of, and were at times so severe that patients could not rise from bed in the morning or raise their arms high enough to dress their hair. Minor symptoms complained of included headache, dizziness, drowsiness and epistaxis. In some cases the prodromal period was so short as scarcely to deserve the name.

Symptoms at the Height of the Attack.—The symptoms at the height of the attack were essentially those of the prodromal period, continued with gradually decreasing severity through the early days of the icterus. This was especially true of the gastro-intestinal phase. Two patients, however, noticed actual and surprising relief of symptoms when the jaundice appeared. The disappearance of the jaundice was slow, the average duration in all cases treated and untreated being thirty-seven days. Fever was seldom observed and was prominent only in three cases. No reliable information was available of patients reached by questionnaires. Jaundice varied from a slight tinge to the most intense icterus. Unfortunately, data on the condition of the liver were recorded in only twenty-seven cases, of which 47 per cent. showed definite diffuse enlargement ranging from a palpable edge at the costal margin to an edge 10 cm. below the ribs. Bulging of the anterior surface was noted once. Fifteen of the sixteen patients

with hepatic enlargement had not had palpable livers on first exam-
ination, and in only two, the one with hepatic cirrhosis, did the liver
remain palpable after the attack passed off. In general, the liver
was not examined until after jaundice appeared. Abdominal tender-
ness, equally distributed between the upper and lower right quadrants
and the epigastrium, was definitely present in 39 per cent. of fifty-
four cases examined.

The Laboratory Findings.—The stool varied in color from white
and waxy in one case, through gray and clay color in the majority
of cases, to normal in three cases. Two stools tested for bile showed
its presence. Thirty-five and one half per cent. of forty-one cases
examined showed evidence of renal irritation, usually in the form of
hyaline casts. Bile was usually, though not invariably, present.

Blood urea estimations and renal functional tests were made on
seven patients with normal results in five. In the most interesting
abnormal case the patient developed very severe vomiting and stupor
suggesting uremia during the early days of the attack. He presented
successively 40 mg., 87 mg., 30 mg. and 40 mg. in a period of twenty-
eight days, the highest reading representing the height of the attack.
This patient was a tabetic whose phenolsulphonephthalein return
(intramuscular) had been 55 per cent. In the later cases of the series
and particularly in one which threatened a serious outcome an effort
was made by Dr. Willis L. Lemon to interpret the nature of the
condition in terms of the findings in the duodenal contents.

INTERPRETATION OF THE DUODENAL FINDINGS

From Table 2 it will be apparent that the jaundice was in part
hematogenous. In one patient who was critically ill the readings were
high during the severity of his illness, but returned to normal on his
recovery, denoting that the cell destruction is not persistent. The
hemolysis, as evidenced by the total number of units and particularly
the units of urobilinogen, was in direct proportion to the severity
of the illness of the patient. Two patients who were only indisposed
had normal readings. The degree of anemia bore the same relation-
ship to the severity of the illness as did the hemolysis. The presence
of acholic stools and of bile in the urine gave evidence that the
jaundice was obstructive in type as well as hematogenous. The
fragility of the cells was undisturbed or slightly increased, as might
be expected in patients who had received an arsenical preparation.
The cholesterol readings were insufficient in number and inconclusive.

With reference to the coincidence of jaundice with influenza, it
has been my (Lemon) experience, based on the observation of cases
of influenza and pneumonia seen in the Clinic, that jaundice is a

TABLE 2.—ANALYSIS OF LABORATORY FINDINGS IN EIGHT PATIENTS WITH JAUNDICE

No.	General Health	Duration	Liver	Stool	Urine	Blood Count	Fragility	Cholesterol	Bile Pigments	Bile Pigments After Recovery
288222	Extremely sick patient; emaciated; painless jaundice	5 weeks	Large and tender	Positive for bile	Urobilin but no bile or urobilinogen	Hb.....60% R.B.C...4.25 W.B.C. 22,700 No...200 cells P.....78.5% S.L....13.0% L.L.....5.5% E.......0.5% B.......1.5% N.M....1.0%	Control 0.40-0.32% Patient 0.40-0.30%	Bloor I...103 mg. Bloor II..146 mg. Difference 43 mg. Normal Bloor I Slight increase, no difference (Luden)	Duodenal contents: normal yellow Urobilinogen.....7 × 200 = 1,140 Urobilin......10 × 200 = 2,000 Total No. units........ 3,400	Duodenal contents: normal yellow Urobilinogen.....0 Urobilin 2×200 = 400 Total No. units...400
136432	Recovering from painless jaundice	4 weeks	Slightly tender	Acholic	Bile, urobilin and urobilinogen	....	....	....	Duodenal contents: Urobilinogen.....5 × 200 = 1,000 Urobilin......4 × 200 = 800 Total No. units.........1,800	
298157	Recovering from painless jaundice; lost 14 lbs. in two weeks	3 weeks	....	Positive for urobilin	Bile	Hb.....78% R.B.C...4.7 W.B.C. 5,460	....	....	Duodenal contents: Urobilinogen....4 × 200 = 800 Urobilin......27 × 200 = 5,400 Total No. units.........6,200	
298460	Recovering from painless jaundice, mild type	10 days	Palpable but not tender	Acholic	Moderate amount of bile	Hb.....54% R.B.C...4.81 Normal differential	Control 0.42-0.36% Patient 0.40-0.28% increased fragility	....	Duodenal contents: normal yellow Urobilinogen....3 × 200 = 600 Urobilin......11 × 200 = 2,200 Total No. units.........2,800	
298287	Recovering from painless jaundice	1 week	Tender on pressure	Putty colored; acholic	Bile, urobilin and urobilinogen	Hb.....78% R.B.C...4.8 W.B.C. 7,200 Normal differential	Control 0.42-0.36% Patient 0.36-0.28% increased resistance	Bloor I... 77 mg. Bloor II..145 mg. Normal Bloor I but high difference possibly due to present treatment (Luden)	Duodenal contents: Failure due to light Urobilinogen......0 Urobilin......1,400 Total No. units.........1,400	
288259	Recovering from painless jaundice	....	....	....	....	....	....	....	Duodenal contents: Urobilinogen....2 × 200 = 400 Urobilin......4 × 200 = 800 Total No. units.......1,200 Normal but on upper limit and border line in character	
79724	Able to be at work; jaundice almost disappeared; no treatment for two months	....	....	....	....	....	....	....	Duodenal contents: normal yellow Urobilinogen....1 × 200 = 200 Urobilin......3 × 200 = 600 Total No. units.......800	
314088	Recovering from painless jaundice; sclera still discolored; streptococci found in submaxillary gland secretion	3 weeks	....	Positive for bile	Bile; urobilin faint trace; urobilinogen absent	Hb.....77% R.B.C...4.78 W.B.C. 8,600	....	....	Duodenal contents: fluid, normal yellow Urobilinogen.....0 Urobilin......3 × 200 = 600 Total No. units.......600	
287857	Slight indisposition	1 day influenza 3 weeks before	Not enlarged or tender	Normal	Bile	Hb.....75% R.B.C...4.66 W.B.C. 5,800	0.36-0.28% incomplete, increased resistance	....	Duodenal contents: Urobilinogen.....0 Urobilin......3 × 200 = 600 Total No. units.......600	

relatively unusual complication. The large majority of these cases, however, were not followed up, or were not under observation for any great length of time, so that they do not form satisfactory material for comparison with the material of the present report, nor was the total number of influenza cases observed as large as the series of patients observed in the Section on Dermatology and Syphilology.

Complete recovery without sequels and with a gain in weight was the rule in 90 per cent. of patients. · Of those who fell short of recovery one had a diffuse nephritis, one an anemia, one became dyspneic (cause not known), and two who had had apparently normal hearts on first examination, developed respectively peri-aortitis and mitral endocarditis. Nine per cent. suffered recurrences of jaundice. Of these two died, one of actinomycosis and the other of an unknown cause; a third relapsed while receiving bladder irrigations for cystitis. A fourth, who suffered a slight recurrence. at the end of a course of treatment, was found to have apparently a chronic duodenitis.

Treatment of the Jaundiced Patients.—Antisyphilitic treatment was discontinued temporarily in 66 per cent. of patients. In those in whom it was continued it seemed to exert no marked influence. At the suggestion of Dr. W. H. Goeckermann patients were given tablets of ox-gall, pancreatin, and sodium bicarbonate, the only form of ox-gall available at the time, in an effort to apply the observations of Eppinger on the effect of this substance in diminishing the viscosity of the bile in cholangitis. In twenty-four cases thus treated, with the addition of sodium phosphate, the average duration from the beginning of jaundice was thirty days. In thirty-eight cases in which sodium phosphate alone was given, with general dietetic measures, the average duration was forty-five days. We do not pretend that such an observation constitutes a final demonstration of the utility of this treatment.

Etiology of the Jaundice; Surgical Conditions and Syphilis.—That surgical conditions of the biliary tract played an insignificant part in our series is apparent from the foregoing description of the material. Syphilis was, of course, directly responsible for the condition of a patient who was jaundiced at first examination. Syphilis, if instrumental in producing the jaundice of the remaining cases, would have to take the form of precocious icterus, which is eliminated in all but two cases by the stage of the disease, or occur as a hepatorecidive in an inadequately treated case, or as a Herxheimer response in a liver already involved before treatment was begun. Practically all of our patients had already received an amount of treatment before jaundice appeared which should exclude the possibility of a hepato-recurrence and should likewise render extremely remote the possibility of a Herxheimer flare-up in the affected organ in an otherwise obscure

hepatic involvement. The most forcible argument against a syphilitic etiology, however, consists in the fact that two thirds of the patients recovered during a suspension of antisyphilitic treatment, and not under treatment, and that 23 per cent. of them were, in fact, never treated for syphilis again after their jaundice appeared. Four of our patients with jaundice did not have syphilis. The instrumentality of syphilis in the production of the jaundice observed by us must, therefore, be regarded as all but negligible.

The Relation of Arsphenamin to Jaundice.—The literature of this question accepts tacitly as a test of such a relation the presence of evidences of arsenical poisoning, especially finding the metal in the urine and liver. If this test fails, the claim for arsphenamin etiology loses much of its force. We concede our study to be incomplete in that no such determinations were made for our cases. According to the recent literature arsenic has been conspiciously absent in the urine and in the liver at necropsy. The demonstration of an arsphenamin etiology, however, seems to require further that there shall be some fairly constant relation between the time of administration of the drug, the amount administered, and the onset and severity of the jaundice. Moreover, the administration of arsphenamin to a patient suffering from arsphenamin icterus, should aggravate the condition and lead to serious consequences, or lead fairly constantly to relapse if the patient were recovering.

Jaundice developed in our patients at all periods of time from the day after injection to forty weeks after the last dose of arsphenamin. Table 2 indicates the evenness with which the onset was distributed over a long period and the lack of any distinctive time relation. So irregular a distribution of onset seems to us opposed to the conception of a purely arsphenamin etiology.

The widest differences were apparent in the amount of arsphenamin received by patients who developed jaundice, and equally striking discrepancies occurred between the severity of the jaundice and the amount of the drug administered. Eight of our patients had had from five to twenty-five arsphenamin injections, without developing jaundice, before their treatment was begun in our department. Two patients developed a very severe jaundice after they had received as little as 0.7 gm. On the other hand, a very mild jaundice developed in two patients who had received 5.5 and 6.8 gm., respectively. Seventy per cent. of the patients who developed jaundice had had amounts ranging from 2.2 to 2.7 gm., representing a single course of six injections, covering a period of six weeks. Approximately one fourth of the patients had mild attacks, one half had moderate, and one fourth severe attacks. Twelve per cent. of the cases of jaundice

developed in patients who had received less than 2 gm., and 17 per cent. developed in patients who had received in excess of 5.7 gm. We think it probable that the preponderance of first-course patients (those who received 2.7 gm.) is at least in part explainable by the fact that such patients are much more easily persuaded to keep in touch with the service for observation than are second and third course patients. The usual interim home period in our plan of treatment is four months, which would make it appear that patients who were given their first course of treatment in the summer and early fall developed jaundice in the late fall and in the winter.

TABLE 3.—Distribution of Onset in Relation to Arsphenamin Administration

Time of Onset	Percentage of Patients
While receiving the drug	14
Within from 1 to 4 weeks after receiving the drug	14
Within from 5 to 6 weeks after receiving the drug	0
Within from 7 to 10 weeks after receiving the drug	20
Within from 11 to 14 weeks after receiving the drug	28
Within from 15 to 18 weeks after receiving the drug	8
Within from 19 to 23 weeks after receiving the drug	14
After 23 weeks	2

Fifty per cent. of our patients resumed arsphenamin treatment immediately on their recovery from jaundice, receiving the drug in amounts as large as those used before the attack, without apparent ill effects. Sixteen per cent. of our patients continued their arsphenamin treatment throughout their jaundice, or resumed it while still jaundiced, without apparent ill effect. These two facts in particular seem to us fairly good evidence that the arsphenamin was not the sole or even the principal causative factor in our group.

Relation of Mercury to Jaundice.—Arguments similar to those for arsphenamin apply to the question of the relation of mercury to the jaundice in our series of cases, and facts not unlike those discussed for arsphenamin were elicited. Five of our patients had received no mercury, and one of them had had none for two years and three months. Three had received insignificant amounts ranging from two to five inunctions. Two received inunctions while they were jaundiced without ill effect, two took pills, and one received the bichlorid intravenously twice a week without effect on the jaundice. One third of our patients were taking inunctions at the time their jaundice developed, but this is more easily explainable as a coincidence than as a consequence, since inunctions form the constant interim treatment of the department and a large proportion of the patients were away on home treatment when their · jaundice appeared. No quantitative relation between the amount of mercury received by a given patient and the

incidence of jaundice was apparent. Certain patients who became
jaundiced had received as high as 185 four-gram inunctions. Others
had barely completed their second inunctions. We believe that these
observations effectually exclude mercury from the rôle of exciting
cause.

Evidence for an Infectious Exciting Cause.—The examination of
our group of cases for indications of an infectious etiology disclosed
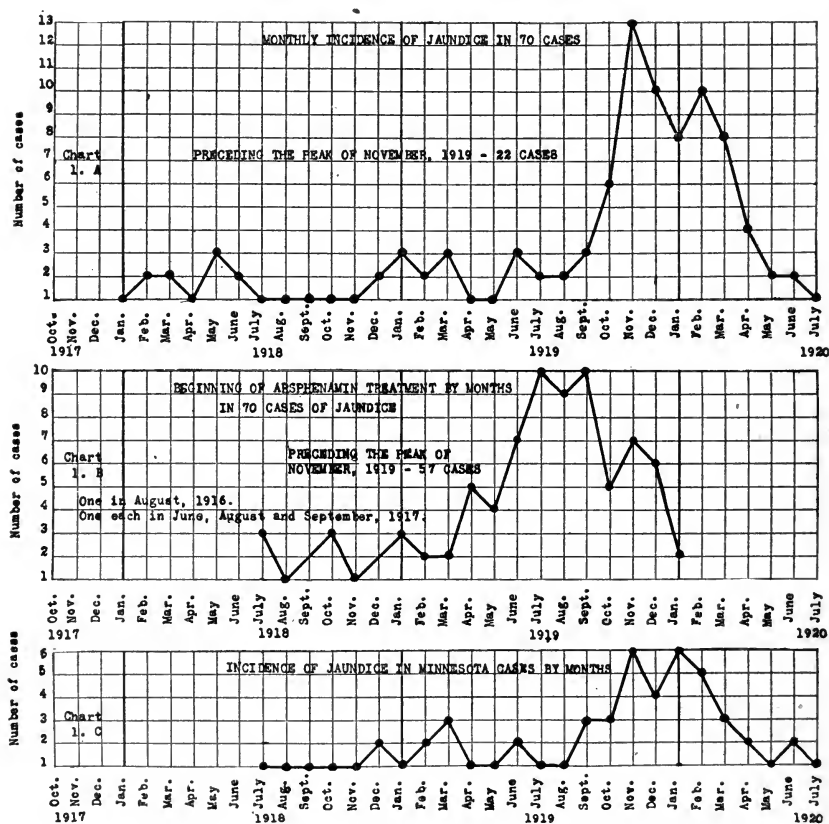
Figure 1

a variety of circumstantial evidence. The overwhelming proportion
of the jaundice occurred between October, 1919, and April, 1920,
with peaks in November and February. This period was one of wide-
spread systemic and respiratory infection, and included the second
wave of epidemic influenza. It is interesting that little or no jaundice
occurred with the epidemic of 1918, which would make jaundice, if
there is any connection with influenza, comparable in a way to lethargic
encephalitis as perhaps a sequel, associate, or modification rather than

a direct complication. The plotted curve of·monthly incidence of jaundice in twenty-nine cases occurring in the state of Minnesota shows the same distribution, in point of time, as the larger series. The second peak in February is identical with the peak of the epidemic influenza wave of the present year (1920).

Chart 1 B, in which is plotted the month in which arsphenamin treatment was begun, when compared with Chart 1 A shows that while 80 per cent. of our patients had received arsphenamin prior to the maximum incidence of jaundice in November, 1919, only 31.5 per cent. had developed jaundice up to that time. It seems probable, therefore, that the remaining 52 per cent. of patients were precipitated into jaundice by some agent that became operative between November, 1919,. and March, 1920. The only other way to explain the acuteness of the rise of the jaundice curve is to consider the possibility of a technical error or a peculiarity of the drug administered. Both possibilities seem to us unlikely on account of the constancy of the technic, the reliability of the product, and the diminishing incidence of other forms of reaction throughout the entire period from January, 1917. The peak of the arsphenamin curve from July to September, 1919, is, we believe, to be explained as incidental to our four months' interim treatment system and the greater ease with which first-course patients as compared with the second and third course patients can be kept under observation and returned.

Further circumstantial evidence for an infectious exciting cause is compiled in Tables 4 and 5.

TABLE 4.—Epidemiologic Relations

	Percentage of Patients
"Colds" and influenza prevalent in vicinity	59
Influenza epidemic (mild) in vicinity	44
Onset of jaundice with nose, throat and respiratory symptoms	41
Jaundice appeared in same town at same time	25
Evidence of direct exposure of patient to jaundice	22
Replies from physicians confirm epidemiologic associations	4 of 6
Total presenting one or another evidence of an infectious character or of association with influenza	73

TABLE 5.—Possible Direct Contacts

	Cases
Jaundice in same household (husband, brother, boarder)	3
Friends and associates jaundiced	4
Jaundice among neighbors	5
Physician and patient jaundiced at same time	1

The replies of physicians, while few in number, deserve more than passing mention. Dr. J. J. Catlin of Buffalo, Minn., stated that he had observed three distinct epidemics of jaundice during the past

fifteen years. The latest one had developed during the late summer and fall of 1919. The symptoms in most cases included coryza, pharyngitis, cough, malaise, fever, vomiting before the appearance of jaundice, pains throughout the body, loss of weight and a light-colored stool. He further remarked, "Some of these cases have been very mild. I have seen families with three cases at a time. There were usually quite pronounced gastro-intestinal symptoms. Occasionally there were families where one or more were jaundiced and another would have the same symptoms and no jaundice." A communication from Dr. George Walker of Roundup, Mont., stated that he had observed three instances of jaundice associated with influenza in about 100 cases but had not observed anything approaching an epidemic. The symptoms associated with the cases of jaundice observed by him included pharyngitis, malaise, fever, vomiting before and after the jaundice appeared, myalgia, loss of weight, clay-colored stools and tenderness over the liver. A communication from Dr. R. B. McBride of Dallas, Texas, stated that he had observed about twice as many cases of jaundice as usual during the past year, but nothing approaching an epidemic. He has noted jaundice following an epidemic of colds. The liver in his cases has usually been palpable and slightly tender. Dr. H. L. Crane of Lead, S. D., in writing with regard to one of our jaundiced patients who was under his care, stated, "I am now of the opinion that his trouble was due to this epidemic form of cholangitis that has been present here for several months. Two of the six reports received from physicians were frankly negative.

SUMMARIES OF CASE REPORTS

The following summaries of cases illustrate a number of suggestive minor circumstances:

CASE 1 (300829).—Following the third arsphenamin injection of the first course, the patient caught cold, developed bronchitis and influenza, then jaundice and double otitis media. Immediately on recovery arsphenamin was resumed; three more injections as large as the first were given without event.

CASE 2 (297229).—The patient developed jaundice twelve weeks after a course of six neo-arsphenamin injections (total 2.4 gm.). The attack lasted three weeks. The patient's wife while nursing him acquired influenza. He has since received a second course of neoarsphenamin, larger dosage than the first, without event.

CASE 3 (287428).—The patient developed jaundice twenty-three weeks after a single course of 2.3 gm. arsenobenzol (six injections). The attack was preceded by a prolonged severe cold. The patient's husband, who had not had antisyphilitic treatment but had accompanied his wife to Rochester, became jaundiced three weeks after the onset of her attack (a frequent incubation period).

CASE 4 (298430).—This patient received six injections of arsphenamin in January, 1920, three months after a patient (Case 3 [287428]) who was a friend of hers, received a similar course. After the second patient returned home, she called on the first patient and found her recovering from jaundice. The sec-

ond patient developed jaundice shortly after, the exact time not being known. This patient states that during this time a number of employees at her husband's office were jaundiced. Both of the patients (Case 3 [287428] and Case 4 [298430]) have since received full courses of arsphenamin treatment without complications.

CASE 5 (270549).—The patient's jaundice began seventeen weeks after the last arsphenamin injection of the first course. This patient, who lived in a small town, went to a neighboring city of 43,000 and was told by his doctor that there were many cases of jaundice and some of sleeping sickness in town. No reply was received from a questionnaire sent to the physician. The onset of this patient's attack consisted of jaundice followed on the second day by signs of a cold and rheumatism in the knees and elbows, and later in the shoulders.

CASE 6 (296919).—This patient had a latent neurosyphilis, with a negative serum Wassermann reaction. No previous treatment had been given. A "tubing reaction" followed the second arsphenamin injection of the first course. The patient was nauseated for one week and then became jaundiced. Her course of treatment was continued with slightly reduced dosage and without ill effect. The liver was not palpable.

CASE 7 (278387).—The patient received three injections of 0.3, 0.4 and 0.3 gm. arsenobenzol and became mildly jaundiced. Jaundice became markedly worse after a spinal puncture and still worse following 0.3 gm. of neo-arsphenamin. Two more injections of 0.4 gm. neo-arsphenamin at the usual weekly intervals were without injurious effect, and the patient began to clear up at the time of her departure from the Clinic. It is possible that the exacerbation following the third injection (neo-arsphenamin) was due to the drug, but since a fourth and fifth larger injections were without effect and a similar exacerbation followed spinal puncture, it seems unlikely that the arsphenamin was responsible.

CASE 8 (177361). (Not included in this series).—The chief operating room nurse of the Section of Dermatology and Syphilology, through whose hands every jaundiced patient seen in the department had passed, after one week of malaise developed a toxic erythema of the face, followed by severe urticaria, which lasted three days. She complained for two weeks of pain and stiffness in the back and shoulders, so severe that she could scarcely rise from bed or dress her hair. She then became slightly jaundiced, with bile in the urine. The liver was not palpable. At no time had she received any form of antisyphilitic treatment, nor had there been anything to suggest gallbladder pathology. A severe pharyngitis developed during the jaundice.

A case illustrative of the fairly sharp distinction that we believe can be drawn between jaundice of late syphilitic origin (hepatic cirrhosis) and the type of acute hepatitis with jaundice discussed in this paper, is the following:

CASE 9 (272613).—A patient with syphilitic cirrhosis of the liver, accompanied by moderate jaundice and with aneurysm of the descending aorta, had nocturnal attacks of substernal pain of great severity. Under mercury by inunction, with neo-arsphenamin injections and massive doses of iodids, he made a striking improvement. His jaundice disappeared, his liver shrank from 15 cm. to 5 cm. below the costal margin, and his aneurysmal pains disappeared. Seven months later (Jan. 21, 1920) after interim mixed treatment by mouth he returned to the hospital in excellent condition for further treatment with inunctions and iodids. Influenza was epidemic in Rochester at this time, a fact which occasioned the patient some uneasiness (this month was also that of the second peak of the jaundice curve). February 3 he complained of rather severe epigastric pain, and was dizzy and nauseated. *There was no*

localized abdominal tenderness. Two days later the gastro-intestinal symptoms still persisted, and he became slightly jaundiced. The jaundice increased to a moderate degree. February 8 there was still considerable epigastric pain and a severe aching pain in the back. Tenderness was now present over the right subcostal region. The liver was markedly enlarged over its usual size and jaundice continued moderate. February 11 the jaundice was clearing rapidly and by February 14 was practically gone, together with his other symptoms, *with the exception of a troublesome cough* that had developed during the attack. A slight loss of weight was apparent, but recovery was otherwise complete. At no time was the patient febrile. During the jaundice, inunctions had been discontinued, and no other antisyphilitic treatment was given. Inunctions were resumed when the jaundice disappeared and ten more had no effect in producing relapse.

Comment: Since no arsphenamin was administered and mercury was resumed without ill effect, it seems unlikely that these drugs were responsible. Since the patient had had considerable treatment previously, and recovered from his jaundice while treatment was suspended, a hepatorecurrence does not form a satisfactory explanation. The most probable explanation seems to involve an infectious element, suggested by the systemic symptoms and cough.

Bacteriologic Studies.—Our efforts to identify an infecting organism in these cases were disappointing. Cultures and animal inoculations made from the secretions of the nose and throat in seven early cases yielded only the usual organisms, and no evidence of hepatic involvement appeared in rabbits inoculated with them. A pure culture of *Bacillus mucosus* obtained from Case 8 (177361) produced death in a rabbit with multiple hemorrhage into the muscles. Blood culture from one patient was negative. We believe, in retrospect, that systemic blood culture during the prodromal period deserves further trial. A stool, in a typical case, yielded only the colon bacillus. In view of the findings reported in the literature investigation for paratyphoid organisms should be carried out.

The paucity of our bacteriologic findings, incomplete though our investigations were, accords with the findings in the literature and suggests too the possibility that the invading organism may be one of the familiar quasi-saprophytic types which in normal persons or in times when epidemic infections such as influenza are not prevalent, with their consequent reduction in the general level of resistance of the population, are unable to overcome the resistance of their hosts.

Discussion of the Literature.—Our survey of the literature was intentionally postponed until our impressions had taken form from the evidence at hand. There appears to be much in recent publications to confirm our impression of the existence of an epidemic catarrhal jaundice of nonspirochetal origin. Curiously enough practically no reference to this literature and no consideration of the possibility that this epidemic jaundice may be masquerading as an arsenical complication of antisyphilitic treatment appears in the recent French and

American literature. A vigorous discussion between Milian [1] as a proponent of syphilologic etiology, and Sicard and his collaborators [2] as proponents of arsenical etiology, has found expression in articles during October and November, 1919, in the *Bulletin de la Societé médicale des Hôpitaux de Paris*. Other isolated reports, such as those of Eschbach,[3] have enlarged the supposed field of toxic factors to include mercury. Conspicuous in the American literature have been the articles of Scott and Pearson,[4] Lynch and Hoge,[5] and Bailey and Mackay.[6] Strathy, Smith and Hanna [7] in the British literature have also discussed delayed arsenical poisoning on the basis of fifty-eight cases following arsphenamin administration. Sicard argues, as have we, that the amount of treatment received by many of the patients under his observation precludes the possibility of hepatorecidives and Herxheimer phenomena as the cause of their jaundice. Treatment in some of his cases frequently included as high as 10 gm. neo-arsphenamin. Milian, on the other hand, points out, with equal justice, that if arsphenamin treatment is continued throughout the period of jaundice the patient will recover. He argues that this constitutes a therapeutic test and demonstrates beyond question the syphilitic character of jaundice. We again find ourselves in accord with Milian's observations but not with his conclusions, since a number of our patients recovered under the continuation of treatment for syphilis. The partial character of the views expressed, seems to be due to the small number of cases observed by each author, which affords little opportunity to appreciate the variety of possibilities involved.

1. Milian, G.: Trois cas d'ictère au cours du traitement a l'arsenobenzol, leur nature syphilitique, Bull. et mém. Soc. méd. d. hôp. d. Par. **43**:821, 1919.

2. Sicard, Haguenau, and Kudelski: L'ictère tardif post-novarsenical et le traitement novarsenical par petites doses repetées, Bull. et mém. Soc. méd. d. hôp. de Par. **43**:880, 1919; Traitement de la syphilis nerveuse chronique. Les éléments de controle de la médication novarsenicale, Bull. et mém. Soc. méd. d. hôp. de Par. **43**:833, 1919.

3. Eschbach, M. H.: Contribution au rôle du novarsénobenzol dans les ictéres chez les syphilitiques et dans les dyscrasies sanguines, Bull. et mém. Soc. méd. d. hôp. d. Par. **43**:1120, 1919.

4. Scott, G. O., and Pearson, G. H. J.: A Preliminary Report on Syphilitic and Arsenical Jaundice, Am. J. Syphilis **3**:628, 1919.

5. Lynch, T. J., and Hoge, S. F.: Toxic Jaundice Following "Intensive" Antisyphilitic Treatment, J. A. M. A. **73**:1687 (Nov. 29) 1919.

6. Bailey, C. V., and MacKay, A.: Toxic Jaundice in Patients Under Antisyphilitic Treatment: A Study of the Chemical Analyses of the Blood and Urine, and Observations on the Effect of Exercise and Diet in the Treatment of Syphilis, Arch. Int. Med. **25**:628 (June) 1920.

7. Strathy, G. S., Smith, C. H. V., and Hannah, B.: Delayed Arsenical Poisoning: A Report of Fifty-Eight Cases Following the Administration of "606" Preparations, Journal-Lancet **1**:802, 1920. Also: Canad. M. A. J. **10**:336, 1920.

Lynch and Hoge [5] reported three cases of jaundice occurring recently during treatment for syphilis, one of which came to necropsy. These authors frankly concede that no traces of arsenic could be found in the liver of the patient coming to necropsy or in the urines of any of the three. Notwithstanding this negative finding they attribute a hepatitis, amounting in their fatal case to almost complete destruction of the liver parenchyma, to antisyphilitic treatment. That the therapy which they described as intensive is by no means the most intensive technic employed was subsequently pointed out by Pollitzer.[8] It may not be out of place at this point to call attention to the fact that the prodromal symptoms in their Cases 2 and 3 were very similar to the typical picture in our series. The jaundice in Case 2 did not appear until thirteen weeks after the course of treatment. Their survey of the literature naturally did not include a number of articles which have become available since the publication of their findings. They note, however, that Fenwick, Sweet and Lowe [9] were likewise unable to demonstrate arsenic in the urines of patients whom they reported as dying of icterus gravis following the injection of neoarsphenamin. The possibility of an infectious epidemic factor in the jaundice is apparently not considered by Lynch and Hoge.

Scott and Pearson [4] in their consideration of syphilitic and arsenical jaundice direct attention to the conventional types of early and late syphilitic and arsenical jaundice already recognized. They do not, however, mention the possibility of an incidental intercurrent infectious jaundice nor do they interpret their findings in the light of this possibility. They apparently accept the view that jaundice occurring during treatment for syphilis must be due to syphilis or arsenic.

In a series of forty cases very carefully studied by Bailey and Mackay with particular reference to the laboratory findings, these authors likewise note the entire absence of arsenic in the urine of all patients examined, at periods ranging from 25 to 157 days after the last arsphenamin administration. They apparently attribute the jaundice to antisyphilitic treatment and suggest as an explanation of the delayed effect the possibility that each dose inflicts a certain amount of injury to the liver, the ultimate acute explosion being induced by the removal of dietetic and physical restrictions when the period of treatment is ended. These authors also apparently do not consider the possibility that an acute infection may serve as an exciting cause of reaction on the part of a therapeutically damaged liver. Their series of cases includes a case of probable syphilitic hepatitis (Case

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8. Pollitzer, S.: "Intensive" Antisyphilitic Treatment, J. A. M. A. **73**:1852 (Dec. 13) 1919.

9. Fenwick, P. C., Sweet, G. B., and Lowe, E. C.: Two Fatal Cases of Icterus Gravis Following Injections of Novarsenobillon, Brit. M. J. **1**:448, 1918.

1) and a case of jaundice (Case 24) without evidence of syphilis or treatment for it. A number of their patients apparently developed exfoliative dermatitis in association with the jaundice, which in our opinion certainly strengthens the view that the jaundice was of arsenical origin. On the other hand we have been impressed with the fact that exfoliative accidents in the course of arsphenamin administration can be precipitated by acute infections such as tonsillitis. Three of our patients had eruptive manifestations and a fourth, with neither syphilis nor treatment for it, had a prodromal erythema and urticaria. Michelson [10] has likewise mentioned the coincidence of streptococcal septicemia and exfoliative dermatitis in a patient under treatment for syphilis.

Evidence pointing to the existence of a nonspirochetal epidemic form of jaundice has likewise been accumulating in the literature of the past year. In December, 1919, Guiteras [11] reported an epidemic of febrile jaundice, at first confused with yellow fever, occurring in the island of Barbados in 1919. This jaundice was associated with albuminuria. Guiteras, in summing up the literature, says that epidemic febrile and infectious jaundice has been more prevalent all over the world in recent years than formerly. In Japan and Flanders the epidemic seems to have been spirochetal in origin, but in Egypt and the Gallipoli peninsula a paratyphoid infection seems to have been the probable cause.

Lindstedt,[12] in April, 1919, illustrates with a series of eight cases the symptomatology and incubation period of a nonspirochetal form of catarrhal jaundice with examples of its probable transmission from patient to patient. The incubation period in his cases varied from two to four weeks but he believes it may be longer. The similarity of this observation to our own data on the prodromal period is evident. Lindstedt believes the entity to be clinically, bacteriologically and epidemiologically distinct from Weil's disease.

In May, 1919, Willcox [13] in his third Lettsomian lecture discusses recent experience with epidemic catarrhal jaundice. He points out that a mild and a grave form are recognizable and that in Mesopotamia and the Dardanelles the jaundice curve attained its maximum about three weeks after dysentery. The epidemic character appeared to be due to a common cause rather than to spread from person to person. This same observation seems somewhat applicable to our

10. Michelson, H.: Discussion, J. A. M. A. **73**:905 (Sept. 20) 1919.

11. Guiteras, J.: Epidemic of Febrile Jaundice in Barbados in 1919, New Orleans M. & S. J. **72**:360, 1919.

12. Lindstedt, F.: Zur Kenntnis des Icterus catarrhalis und dessen Inkubationszeit, Deutsch. med. Wchnschr. **45**:434, 1919.

13. Willcox, W. H.: Epidemic Catarrhal Jaundice, Lancet, **1**:930, 1919.

cases. A paratyphoid organism was identified by Sarailhé and Clunet.[14] No evidence of a spirochetal origin could be found in spite of much effort. Willcox believes that epidemic catarrhal jaundice is probably due to an intestinal infection causing duodenitis and a catarrh of the bile duct. He believes it to be associated with a transient bacteremia of which the causal organism is yet to be proved. These suggestions impress us as very much to the point.

In July, 1919, Tooth and Pringle [15] reported an epidemic of catarrhal jaundice occurring among British troops in Italy involving in all 111 cases. Two types were recognized, one with pyrexia and the other without. The seasonal incidence was overwhelmingly during September and October, 1918. In the milder cases the symptoms were usually pain in the epigastrium and indisposition, headache, nausea, vomiting, general malaise, and diarrhea. In the pyrexial cases, general pains, epistaxis and sore throat were noted and diarrhea was rare. In two cases inoculations of guinea-pigs for *Spirochaeta icterohemorrhagica* were positive but in a large number of other cases similar inoculations were negative. This leads the authors to believe that the pyrexial form of jaundice was probably due to spirochetal infection although they suggest the possibility of a relation to epidemic influenza, which was prevalent in Italy during these months.

In June, 1919, Bronson [16] reported the association of jaundice with influenza in children and at the same time Roussel and de Lavergne [17] reported five cases of jaundice associated with nephritis in a pneumococcal infection in which the organism was demonstrated in the blood. These cases occurred in January and March, 1919, during periods of recrudescence of an epidemic of "grippe." In September and October, 1919, Quenu, Küss and Brulé [18] called attention to the difficulty of recognizing cases such as the one they described, in which recurring attacks of fever with jaundice suggested angiocholitis except

14. Sarailhé, A., and Clunet, J.: La "Jaunisse des camps" et l'épidémie de paratyphoide des Dardanelles, Bull. et mém. Soc. méd. d. hôp. d. Par. **40**:45, 1916.

15. Tooth, H. H., and Pringle, E. G.: Jaundice Among the British Troops in Northern Italy, Lancet **2**:144, 248, 1919; Supplementary Note on Jaundice Among the British troops in Northern Italy, Medico-psychological Association of Great Britain and Ireland: The annual meeting, Lancet **2**:248, 1919.

16. Bronson, E.: Catarrhal Jaundice Associated With Influenza in Children, Brit. J. Child. Dis. **16**:73, 1919.

17. Roussel, M., and Lavergne, M.: Cinq cas d'ictère par hepatonephrite, secondaire à une pneumococcie grippale. De la presence du pneumocoque dans le sang des ces malades, interpreté comme un signe de retention biliare dissociée, Bull. et mém. Soc. méd. hôp. de Par. **35**:587, 1919.

18. Quénu, E., Küss, G., and Brulé, M.: Septicémie à streptocoque non hémolitique accompagnée d'ictère et simulant une angiocholite lithiasique, Rev. de chir. **57**:785, 1919.

for the absence of gall stone colic pains, the streptococcus being found in the blood. In this connection it is interesting to recall certain of our own cases of recurrence.

The first discussion of acute epidemic jaundice which has come to our attention in recent American literature is that of Symmers.[19] During a period of ten weeks commencing in December, 1919, he stated that sixteen patients were admitted into Bellevue Hospital with severe jaundice, of whom 56.2 per cent. died. Symmers mentions moreover that he has observed a notable excess of cases of acute catarrhal jaundice during the past year. In eight of his cases search was made by various methods for a spirochetal organism but nothing could be found. In three of the patients who died with symptoms of acute yellow atrophy of the liver, chemical examination for heavy metals was negative. From Symmer's description we are inclined to believe that we have been dealing in most of the cases under our observation with an essentially similar process, though as a rule much less severe. He particularly notes the occurrence of lassitude, digestive disturbances, and signs indicative of bronchitis. Two of his patients were operated on under the impression that they were suffering from a surgical obstructive jaundice. Symmers points out in his study of the pathology that the destructive changes in the liver may so closely resemble acute yellow atrophy as to be indistinguishable in the gross. The type of jaundice discussed by Symmers was often hemorrhagic in character. In only one of our cases, however, was there a distinct purpuric eruption.

It will be apparent from the foregoing summary of the literature that an epidemic and possibly infectious form of catarrhal jaundice has been gradually coming to medical attention during the period in which we have been suspecting an infectious etiology for our cases. Attempts to identify a causative organism for this type of jaundice have not evidently thus far been entirely successful.

Due weight should be given to the possibility that without being the direct cause of hepatitis and jaundice, epidemic infections such as influenza, create widespread states of hypersusceptibility which result in the breakdown of tissues and organs subjected, as the liver is in antisyphilitic treatment, to therapeutic strains which are ordinarily borne without reaction. We have for several years past been impressed with the importance of this element in mercurial stomatitis, in renal reactions, and in the general course of syphilis, treated and untreated. Such a view would make infection a predisposing cause and arsphenamin and mercury the exciting cause of the jaundice we have observed.

19. Symmers, D.: Epidemic Acute Hemorrhagic Jaundice of Toxic Origin, J. A. M. A. **74**:1153 (April 24) 1920.

The fact that the connection between arsphenamin, mercury, and the jaundice so often seems remote in time and quantitative relations, and that a further administration of these drugs so often is without injurious effect, makes this, in our estimation, a much less plausible theory than that of an infectious exciting cause.

We believe that the group of cases here presented serves to connect, in a measure, the general observations on epidemic catarrhal jaundice and observations such as those of Lynch and Hoge and other writers [20] who have sought to ascribe jaundice to the injurious effects of antisyphilitic treatment. Unquestionably, a certain amount of confusion has arisen in the literature from the fact that cases of undoubted syphilitic and arsenical jaundice, and of jaundice from surgical obstructive factors must occur in groups of patients under treatment for syphilis. So far as our own experience goes we believe that all the facts can be satisfactorily explained on the theory that a relatively small proportion are syphilitic and arsenical in origin, or have surgical conditions underlying them, but that the rôle of antisyphilitic treatment is usually only incidental and predisposing. The real cause of the great excess of cases of jaundice in our present experience as compared with our former seems to be, at least on the clinical evidence presented, the intervention of an extraneous, probably infectious, factor.

SUMMARY

1. Jaundice as a complication of the treatment of syphilis in the Section on Dermatology and Syphilology of the Mayo Clinic was a relatively rare occurrence during the period from August, 1916, to August, 1918. From August, 1918, to July, 1920, the incidence of this complication has increased over 1,000 per cent.

2. During the period from January, 1917, to July, 1920, there have been no notable changes in the technic of routine treatment of syphilis in this section, and one of the most reliable brands of arsphenamin and neo-arsphenamin has been consistently employed throughout the entire period, with a steady diminution of other types of complications. Neither have there been any conspicuous changes in the types of syphilis treated.

3. It is scarcely reasonable, therefore, to conclude a priori, that because most of the patients had syphilis and were treated for it, either syphilis or antisyphilitic treatment was responsible for the enormous increase in the incidence of jaundice among them. This

20. Eppinger, H.: Weitere Beiträge zur Pathogenese des Ikterus, Beitr. z. path. Anat. u. z. allg. Path. **33**:123, 1903; Ikterus, Argebn. d. inn. Med. u. Kinderh. **33**:107, 1908.

increase amounted to four times the maximum expectancy of jaundice as a complication according to the Meirowsky statistics based on 225,780 injections.

4. A critical examination of the data obtained from the seventy cases occurring among our patients indicates that while several distinct types of jaundice are probably represented in the series, the large proportion were not ascribable directly if at all to the effects of syphilis, or of antisyphilitic treatment with either arsphenamin or mercury.

5. Syphilis as either a primary or a secondary etiology is largely excluded by the fact that the overwhelming proportion of the patients had had so much treatment before jaundice that Herxheimer effects and hepatorecurrences were practically eliminated.

6. Moreover, two-thirds of the patients recovered while antisyphilitic treatment was suspended, and one-fourth of those who recovered were in fact not again treated for the disease after the jaundice appeared. Four of the patients who were jaundiced did not have syphilis.

7. The argument against an arsphenamin etiology is based on the fact that no definite time sequence between the administration of arsphenamin and the incidence of jaundice can be detected, jaundice often appearing so late that any connection between the two occurrences is merely a matter for speculation. There was no constant relationship between the total dosage of arsphenamin administered and the severity of the hepatic symptoms which could not be largely explained on the basis of the time intervals in the interim home treatment system of the department. Arsphenamin had almost no unfavorable effect on those patients who continued it during their jaundice (16 per cent. of the series), and resumption of the arsphenamin in 50 per cent. of our patients as soon as their jaundice cleared up had no effect in producing relapse. Jaundice occurred in patients receiving neo-arsphenamin in isotonic solution, as well as in those receiving arsphenamin, so that a hemolytic influence of the drug seems not to be a factor.

8. Similar arguments applied in demonstrating the probable lack of relation between the adminstration of mercury and the incidence of jaundice lead to similar conclusions. Six of the jaundiced patients had never received mercury and several others had had insignificant amounts. Three received it throughout their jaundice without ill effect.

9. The study of this series of seventy cases discloses strong circumstantial evidence to the effect that an infectious agent, possibly associated with epidemic respiratory infections, is the exciting cause of the wave of jaundice observed since August, 1919.

10. The overwhelming proportion of the incidence of jaundice occurred between October, 1919, and April, 1920, with peaks in November and February. Prior to November, 1919, 80 per cent. of the seventy patients had received arsphenamin, but only 31.5 per cent. had developed jaundice. The remaining 52 per cent. not thus far jaundiced were, therefore, precipitated into the complication between November and April by some extraneous factor.

11. The months of maximum incidence of jaundice were those of epidemic respiratory and systemic infection, including influenza.

12. Forty-one per cent. of the patients of our series had coryza, tonsillitis, pharyngitis, influenza, "grippe," bronchitis, pneumonia or otitis media (named in order of frequency), intimately associated with the prodromal symptoms or actual appearance of the jaundice.

13. Symptoms suggestive of a systemic infection, with lassitude, arthritis and myalgia, backache, anorexia, nausea and vomiting, diarrhea or constipation, headache, dizziness, loss of weight, and non-localizable abdominal distress, usually preceded by several days or weeks, the onset of the jaundice and of hepatic symptoms as such.

14. The administration of ox-gall in tablet form seemed of some benefit in shortening the course of the jaundice in twenty-four of our cases.

15. Fifty-nine per cent. of our cases were associated with epidemics of colds and influenza in the vicinity.

16. One-fourth of the patients gave histories of jaundice developing in their localities, often in relatives, neighbors, and friends.

17. Four of six physicians testified to an association of jaundice with coryza, pharyngitis, and influenza in their recent experience. Two testified to epidemic features during the months included in our survey.

18. A total of 73 per cent. of our cases yielded one or another contributory evidence of a possible infectious factor in the etiology of the jaundice.

19. Incomplete bacteriologic studies of seven cases were unsuccessful in identifying a causative organism.

20. Study of the recent literature after our impressions were formed supplied confirmatory evidence that a form of nonspirochetal catarrhal jaundice of unknown etiology is coming into medical recognition, and has at various times and places in this country, Europe, and Asia, attained to epidemic proportions. This type of jaundice exhibits many of the salient features presented by the large proportion of our cases.

21. The possibility that this type of jaundice may be masquerading as syphilis or as an arsenical complication of antisyphilitic treatment

has been overlooked by recent writers on the subject, and undue aspersion, perhaps, has been cast on modern syphilotherapeutic methods. This is especially true since no arsenic could be found in the urines nor in the livers in necropsied cases. This apparently epidemic jaundice is associated with a hepatitis often closely simulating that produced by the heavy metals.

22. Laboratory studies and the literature suggest that the jaundice is, in part, hemotogenous and associated with gastro-intestinal lesions.

23. The intensity of the hemotogenous phase is proportional to the illness of the patient and is mild or absent in mild attacks.

24. The relation between influenza and the type of jaundice discussed is problematical. Little or no jaundice appeared among our patients during the influenza epidemic of 1918, and the time of incidence of the complication in 1919 and 1920 has been approximately but not exactly that of influenza. About 400 cases of influenza observed in the Clinic by one of us (Lemon) showed no special tendency to develop jaundice as a complication. It must be recalled, however, that the seventy cases here considered were collected from among a total of 5,200 patients. It is possible that the condition is a sequel or modification of epidemic influenza, rather than a direct complication.

25. We do not regard our contentions as proved conclusively. We believe, however, that while any agent potentially injurious to the parenchyma of the liver, such as arsphenamin, may, and probably does, act as a predisposing cause in the cases of hepatitis that have recently become so comparatively numerous in our experience, the exciting cause is probably an as yet unidentified infectious agent. This agent may be responsible for varying grades of hepatitis, ranging from mild cholangitis to extensive destruction of the affected organ, suggesting acute yellow atrophy.

OBSERVATIONS ON THE PATHOLOGIC PHYSIOLOGY OF CHRONIC PULMONARY EMPHYSEMA *

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The object of this paper is to record the results obtained from experiments on two patients with chronic pulmonary emphysema, of the so-called "large lunged" type. The work was undertaken in an effort to ascertain facts which might lead to a clearer appreciation of the disturbance in respiratory physiology in emphysema.

The gross and microscopic appearance of the lungs in this condition is well defined; also the impediment to the mechanics of respiration afforded by the loss of the elastic tissue of the lungs is appreciated. Further investigation, however, is necessary to show to what extent the degenerative process interferes with the aeration of the blood and the manner in which the body adapts itself to the altered conditions.

The work of Siebeck,[1] Porges, Leimdorfer and Markovivi,[2] Hoover[3] and others established the fact that the residual air and the functional dead space are increased, while the vital capacity is much diminished. Such changes naturally interfere with the alveolar ventilation and cause the patient with emphysema to suffer from a certain amount of pulmonary insufficiency particularly evident when a demand for increased gaseous exchange is to be met, as in exercise.

Another fact noted by most workers is the abnormally high tension of carbon dioxid maintained in the alveolar air. Different explanations have been offered for this. Recently, in experiments on dogs, Friedman and Jackson[4] found that there was an elevation in the carbon dioxid content of both the alveolar air and blood, when expiration was obstructed. This was attributed to the interference to the pulmonary circulation from the high intrabronchial pressure produced. Such elevations in intrabronchial pressure are not seen in patients with emphysema, except during an attack of asthma, or a paroxysm of coughing, when the impairment in the lesser circulation is probably an important factor in diminishing the gaseous exchange in the

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1. Siebeck, R.: Deutsch. Arch. f. klin. Med. **102**:390, 1911.

2. Porges, O., Leimdorfer, A., and Markovici, E.: Ztschr. f. klin. Med. **77**:446, 1913.

3. Hoover, C. F.: Arch. Int. Med. **11**:52 (Jan.) 1913.

4. Friedman, E. D., and Jackson, H. C.: Arch. Int. Med. **19**:767 (June) 1917.

lungs. Other causes, therefore, must be considered in order to explain the high carbon dioxid content of the alveolar air in subjects with emphysema. These individuals may be comfortable and able to walk about tolerating in the alveolar air a percentage of carbon dioxid which would cause profound hyperpnea in a normal person. With no convincing evidence to the contrary it may be assumed that in such individuals the alveolar carbon dioxid is in equilibrium with the free carbon dioxid in the arterial blood. Recalling the well established physiologic relation between the activity of the respiratory center and the level of free carbon dioxid in the blood, it is at once apparent that the subject with emphysema represents a wide departure from the normal. For example, such patients have been observed to be perfectly comfortable when breathing from 8 to 10 liters of air per minute, with the alveolar carbon dioxid about 8 per cent.

After noting the unusual tolerance to carbon dioxid in several patients it was decided to study quantitatively the respiratory response to increasing percentages of carbon dioxid in the inspired air. The data thus obtained were compared to those found under similar experimental conditions in normal resting individuals. Two hospital patients with well marked chronic pulmonary emphysema were selected for this study. They were free of myocardial disease as far as could be determined clinically and with the aid of the electrocardiograph and at no time, since first observed, have any myocardial symptoms appeared. Particular attention has been paid to the circulation to eliminate as far as possible the effect of pulmonary stasis on the experimental results. The frequent association of myocardial disease with pulmonary emphysema has obviously limited the number of available subjects.

<div align="center">REPORT OF CASES</div>

CASE 1.—Eli B., male, aged 46 years, first came under observation in March, 1913, suffering from an attack of acute bronchitis. At that time he had definite pulmonary emphysema with a slight degree of cyanosis which persisted after recovery from bronchitis. He was not seen again until March, 1919, when he was admitted to the hospital complaining of cough and shortness of breath. The chest presented the typical "barrel-shaped" conformation with an increase in all diameters, particularly the anteroposterior diameter. There was narrowing of the subcostal angle during inspiration. The expiratory phase of respiration was prolonged and on auscultation numerous râles were heard throughout both lungs. No cardiac enlargement was demonstrable. The heart sounds were normal and there was no evidence of venous stasis, except during a paroxysm of coughing when the veins of the neck became very prominent. The blood pressure was 130 mm. systolic and 90 mm. diastolic. There was definite clubbing of the fingers. The cyanosis of the face and hands was quite marked for a few days after admission to the hospital but appreciably diminished as he recovered and was able to walk about comfortably, but even then the lips and finger nails presented a dusky, blue appearance. The patient had no fever at any time and the urine was normal.

CASE 2.—Peter W., male, aged 49 years, has been in the hospital since first admitted in January, 1919. His complaint was shortness of breath and cough. Inspection showed the typical emphysematous thorax, with cyanosis of the face and hands. No pulmonary consolidations were found but a diffuse bronchitis was present throughout both lungs. The patient was apparently having much difficulty in ventilation, and expiration lasted about three times as long as inspiration. Marked narrowing of the subcostal angle occurred with inspiration. The blood pressure was 120 mm. systolic and 80 mm. diastolic. After ten days in bed the patient was much improved and has since been able to walk about fairly comfortably. A slight degree of cyanosis of the lips and mucous membranes of the mouth has persisted. Figure 1 shows the conformation of the thorax.

Fig. 1.—Patient Peter W., showing the conformation of the thorax.

RESPIRATORY RESPONSE TO CARBON DIOXID IN TWO NORMAL
INDIVIDUALS COMPARED WITH TWO PATIENTS
WITH CHRONIC PULMONARY EMPHYSEMA

Description of Apparatus Used.—The subject is comfortably seated in a chair before which is a small adjustable table that may be readily placed on a level with the mouth. Projecting over the edge of this table is a rubber mouthpiece connected with a pair of gut valves. These valves [5] have been adopted in preference to others tried, because they are the most efficient and cause a minimum impediment to the

5. The technic of making the valves has been described by Pearce: Am. J. Physiol. **44**:369, 1917.

free ingress and egress of air. The subject inspires from a large 240 liter spirometer and expires into a smaller type of spirometer of 100 liters capacity. These spirometers are of the Tissot model, equipped with an eccentric wheel at the top so that the bell is counter-poised at all levels by means of a weight. Cylinders delivering carbon dioxid and oxygen through a Bohr meter into the inspiratory spirometer make it possible to prepare rapidly any desired concentration of the two gases for the subject to breathe. The bell of the inspiratory spirometer is so weighted that it tends to fall very slowly when opened to the air. Similarly the bell of the spirometer into which the subject expires is so balanced that it rises slowly when opened to the air, thus assisting the expiration. Attached to both spirometer bells is a small pointer which moves along a graduated scale at the side, showing the exact amount of air in the spirometers at any position of the bell. Non-collapsible rubber tubing connects the respiratory valves with the two spirometers. Both the tubing and the spirometer pipes are one inch inside diameter. On the intake pipe of the expiratory spirometer is a three way metal valve. By this arrangement the subject's expired air can be directed either into the room or into the spirometer. Samples of air for analysis are drawn off through an opening at the top of the spirometer bells. The gas analyses are made with the well known Haldane apparatus.

Technic of Experiments.—The subject is brought to the laboratory and allowed to rest for thirty or forty minutes. He then assumes a comfortable position in a chair and the small table is so adjusted that the rubber mouthpiece connected with the respiratory valve can be held in the mouth with a minimum of muscular effort. The nose is closed with an ordinary nose clip; the subject now inspires from the large spirometer filled with room air and expires through the three way valve into the room. This preliminary period in which from fifty to sixty liters of air are breathed affords the subject time to accustom himself to the experimental conditions. After inspecting the respiratory valves and other parts of the apparatus, the time is noted and the expired air is allowed to enter the spirometer. The experiment is continued usually for five minutes or less, depending on the minute volume of the subject's respiration. The nose clip and mouthpiece are now removed and the subject breathes naturally until the next experiment. This interval is about fifteen minutes during which the analysis of the expired carbon dioxid is made and the inspiratory spirometer is filled with a new mixture and analyzed. At least two observations at room air are first made to see that the carbon dioxid output is fairly constant. Other experiments with various percentages of carbon

dioxid in the inspired air are then made. Sufficient amounts of oxygen have always been added to maintain its concentration in the inspired at approximately 20 per cent.

Respiratory Response to Carbon Dioxid.—The results obtained on the two normal individuals are presented in Table 1. These data show the approximate variations that have been found in normal resting persons after they have become accustomed to the experimental conditions. Even individuals such as medical students who understand the purpose of the experiments are very likely to over-ventilate at the first few observations. The same is, of course, true of hospital patients, but after a little experience constant results are obtained.

TABLE 1.—The Respiratory Response to Increasing Percentages of Carbondioxid in the Inspired Air in Two Normal Subjects

| Inspired Air | Period Observed, Min. | Total Volume Expired Air, Liters | Minute Volume Expired Air, Liters | Carbon Dioxid | | | Respiratory Rate per Min. |
				Expired, per Cent.	Expired per Minute, C.c.	Inspired per Minute, C.c.	Output over Intake, C.c.	
Subject C. P. H.								
Room air.........	5	25.5	5.1	4.40	224	0	224	8
Room air.........	5	25.0	5.0	4.64	232	0	232	7
1.7% CO_2.........	5	35.5	7.1	5.12	363	120	243	8
3.04% CO_2........	5	44.0	8.8	5.44	479	268	211	10
4.5% CO_2.........	4	48.0	12.0	5.84	701	540	161	13
6.16% CO_2........	3	58.5	19.5	7.04	1,373	1,201	172	17
7.2% CO_2.........	2	70.0	35.0	7.60	2,660	2,520	140	25
Subject P. J. C.								
Room air.........	5	35.0	7.0	3.44	241	0	241	17
Room air.........	5	35.0	7.0	3.40	238	0	238	17
1.92% CO_2........	5	40.0	8.0	4.32	346	154	192	15
4.0% CO_2.........	5	56.0	11.2	5.76	645	448	197	15
6.0% CO_2.........	3	52.5	17.5	7.00	1,225	1,050	175	17
7.12% CO_2........	2	44.0	22.0	7.84	1,725	1,566	159	18
8.40% CO_2........	2	64.0	32.0	8.80	2,816	2,688	128	22

Table 2 contains the results of two experiments on Eli B., a patient with chronic pulmonary emphysema. The experiment made April 5 was done shortly after his admission to the hospital and shows a sluggish respiratory response to inspired carbon dioxide. Similar results were obtained in the experiment done five months later (Sept. 13). A comparison of these two experiments shows the constancy with which the abnormal response to carbon dioxid is maintained. A further illustration of this is given by the data in Table 3. These experiments were performed several months apart on Peter M. This patient has been in the hospital all this time and frequent observations at intervals have yielded similar results. His respiratory response to carbon dioxid and that of the normal subject, P. J. C., is shown graphically in Figure 2.

After observing the respiratory response to carbon dioxid in normal individuals and particularly in patients with heart disease, the subjects

TABLE 2.—THE RESPIRATORY RESPONSE TO INCREASING PERCENTAGES OF CARBON DIOXID IN ELI B., A PATIENT WITH CHRONIC PULMONARY EMPHYSEMA

Inspired Air	Period Observed, Min.	Total Volume Expired Air, Liters	Minute Volume Expired Air, Liters	Carbon Dioxid				Respiratory Rate per Min.
				Expired, per Cent.	Expired per Minute, C.c.	Inspired per Minute, C.c.	Output over Intake, C.c.	
Experiment 1 April 5, 1919								
Room air..........	5	45.0	9.0	3.88	349	0	349	17
Room air..........	5	44.5	8.9	3.84	342	0	342	18
1% CO₂............	5	45.5	9.1	4.32	393	91	302	19
2.32% CO₂........	3	27.5	9.2	5.44	500	213	287	18
5.52% CO₂........	4	44.0	11.0	7.52	827	607	220	18
7.08% CO₂........	3	42.5	14.2	8.68	1,233	1,005	228	19
8.00% CO₂........	3	50.0	16.6	9.32	1,547	1,328	219	21
9.12% CO₂........	3	57.0	19.0	10.32	1,960	1,732	228	22
Experiemnt 2 Sept. 13, 1919								
Room air..........	5	40.0	8.0	4.20	336	0	336	11
Room air..........	5	37.5	7.5	4.28	321	0	321	12
1.6% CO₂..........	4	35.0	8.8	5.12	450	140	310	15
3.84% CO₂........	4	36.0	9.0	6.80	612	346	266	12
6.32% CO₂........	3	37.5	12.5	8.40	1,050	790	260	18
7.00% CO₂........	3	36.5	12.2	8.80	1,074	854	220	14
8.32% CO₂........	3	44.0	13.7	9.68	1,326	1,140	186	15
9.50% CO₂........	3	49.5	16.5	10.64	1,756	1,568	188	17

TABLE 3.—THE RESPIRATORY RESPONSE TO CARBON DIOXID ON DIFFERENT DATES IN PETER W., A PATIENT WITH CHRONIC PULMONARY EMPHYSEMA

Inspired Air	Period Observed, Min.	Total Volume Expired Air, Liters	Minute Volume Expired Air, Liters	Carbon Dioxid				Respiratory Rate per Min.
				Expired, per Cent.	Expired per Minute, C.c.	Inspired per Minute, C.c.	Output over Intake, C.c.	
Experiment 1 Feb. 22, 1919								
Room air..........	5	37.5	7.5	3.84	288	0	288	20
Room air..........	5	39.5	7.9	3.48	275	0	275	20
1.96% CO₂........	5	39.0	7.8	4.88	381	153	228	20
3.92% CO₂........	5	49.0	9.8	6.16	604	384	220	21
6.08% CO₂........	4	42.5	10.6	7.88	835	644	191	21
7.28% CO₂........	3	33.5	11.2	8.88	994	815	179	21
8.36% CO₂........	3	34.5	11.5	9.80	1,127	961	166	21
9.60% CO₂........	3	35.0	11.7	10.92	1,278	1,123	155	21
Experiment 2 Sept. 16, 1919								
Room air..........	5	37.5	7.5	4.24	318	0	318	20
Room air..........	5	42.0	8.4	3.76	314	0	314	18
2.64% CO₂........	7	68.5	9.8	5.40	529	259	270	21
3.92% CO₂........	5	53.0	10.6	6.32	670	415	255	21
4.96% CO₂........	5	58.5	11.7	7.44	870	580	290	20
6.44% CO₂........	5	61.0	12.2	8.60	1,049	785	264	21
7.52% CO₂........	4	53.5	13.4	9.33	1,250	1,008	242	22
10.45% CO₂........	2	28.0	14.0	11.30	1,639	1,515	124	20
Experiment 3 Oct. 5, 1919								
Room air..........	5	51.5	10.3	3.20	330	0	330	22
Room air..........	5	51.5	10.3	3.24	334	0	334	22
4% CO₂............	3	33.5	11.2	6.16	690	448	242	22
6.12% CO₂........	3	35.5	11.8	8.04	949	722	227	22
8.08% CO₂........	3	38.5	12.8	9.76	1,249	1,034	215	22
9.28% CO₂........	3	39.5	13.2	10.56	1,394	1,225	169	21
10.24% CO₂........	3	42.0	14.0	11.56	1,618	1,434	184	22
11.44% CO₂........	3	42.0	14.0	12.48	1,747	1,607	145	22

with emphysema afford a very sharp contrast. The ease and apparent comfort with which emphysematous patients inspire high percentages of carbon dioxid (from 8 to 10 per cent.) for short periods is very striking. This is, of course, true only up to a certain percentage, which might be called the tolerance level. At or a little above this level, symptoms of acute distress develop quite abruptly. There is
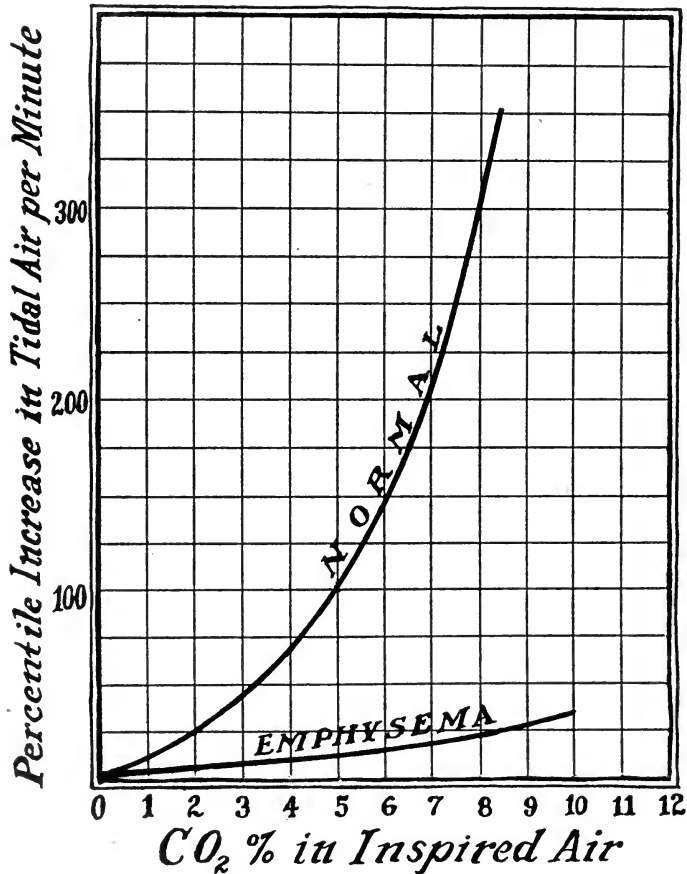

Fig. 2.—This shows the percentile increase in tidal air per minute as the percentage of inspired carbon dioxid is raised. Note that when the normal subject inspires air containing 8 per cent. carbon dioxid, the tidal air is increased about 300 per cent. and in the emphysematous subject only about 25 per cent.

headache, nausea, dizziness and the subject refuses to continue the experiment. This appearance of acute distress at a certain concentration of inspired carbon dioxid is quite characteristic and was noted in all experiments where high percentages were breathed for short periods (from 10 to 15 minutes). Take, for example, experiment 3

in Table 3, which was done particularly to find the tolerance level. While inspiring 9.28 per cent. carbon dioxid the subject was apparently comfortable and made no complaint. Breathing 10.24 per cent. carbon dioxid caused a little dizziness, but the next observation with 11.44 per cent. caused considerable distress and it was with much effort on the part of the subject that the experiment was continued to the end. At this high concentration the minute volume was 14 liters. This and other experiments have indicated that 14 liters per minute is the maximum volume of air which this subject can exchange. In other words, with a potent stimulus to respiration he has a factor of safety amounting to about 7 liters per minute as compared with about 50 liters for normal persons under the same conditions. This indicates a marked limitation in pulmonary reserve. It also shows how helpless the emphysematous subject is to combat an accumulation of carbon dioxid in the body occurring when metabolism is increased as in exercise, or when the resting metabolic carbon dioxid is retained as happens when air rich in carbon dioxid is inspired.

For a given concentration of inspired carbon dioxid the emphysema subjects take less carbon dioxid into the lungs per minute. This is obviously due to the difference in minute volume in the two cases. For example, Peter W. (Table 3) breathing 10.15 per cent. carbon dioxid actually took into the lungs less carbon dioxid per minute than the normal subject, P. J. C. (Table 1), breathing 7.12 per cent. carbon dioxid. It is further noted in both the normal and emphysematous subjects that as the per cent. of inspired carbon dioxid rises, the excess of carbon dioxid output over intake falls. These figures are obtained by simply subtracting the cubic centimeters of carbon dioxid inspired per minute from that expired per minute. Obviously, at room air the difference represents metabolic carbon dioxid but as increasing percentages are breathed more and more metabolic carbon dioxid is retained in the body.

The almost constant respiratory rate at all concentrations of inspired carbon dioxid, particularly in the case of Peter W. (Tables 5, 6 and 7) afford an interesting illustration of the significance of the lung elasticity in breathing. Even while respiring room air there is no time interval between one expiration and the succeeding inspiration. With a potent stimulus to respiration Peter W., is unable to inflate and deflate his lungs more than twenty-two times per minute. It is a matter of common observation that most cases of emphysema have a prolonged expiratory cycle. In both Eli B. and Peter W. expiration lasted approximately twice as long as inspiration.

In comparing the data from the experiments on the two subjects with emphysema it is noted that Eli B. was a little more sensitive to

carbon dioxid. This may have been due in part to the fact that he had a lesser grade of emphysema, as indicated by the size of the lungs and by the diminished vital capacity (Table 4).

TABLE 4.—The Vital Capacity on Different Dates in the Two Emphysematous Subjects

Eli B., Height 5 ft. 9 in.		Peter W., Height 5 ft. 10 in.	
Date	Vital Capaetly, C.c.	Date	Vital Capaeity, C.c.
4/ 2/19	2,600	2/18/19	1,600
4/ 5/19	2,800	4/ 6/19	1,700
4/14/19	3,200	10/ 5/19	1,750

The Carbon Dioxid Tension of the Blood.—It has been demonstrated by others that the carbon dioxid tension in the alveolar air is abnormally high in emphysema. Several experiments were done to determine the alveolar carbon dioxid, using the original Haldane and Priestly technic and also the method brought out by Pearce.[6] The results were usually well above the normal but they showed considerable variation. This was attributed to poor cooperation on the part of the subject. In order to obtain more constant results, the carbon dioxid tension in the blood was determined by analysis of the expired air brought into equilibrium with the venous blood. The method suggested by Henderson and Prince [7] was found most useful in work with patients. The technic is simple and quite consistent results were obtained in both normal and diseased individuals. With this method not only the tension of carbon dioxid in the venous blood is determined, but some information is also obtained concerning the rapidity with which equilibrium is reached between the gases of the venous blood and the air in the lungs. Here, as in the foregoing observations, the data obtained in experiments on normal individuals were used for comparison with those found in the subjects with emphysema. The technic employed was as follows: A graduated Krogh spirometer of six liters capacity is used instead of a rubber bag, as recommended by Henderson. The spirometer is preferred because it affords a means of checking the total volume of each successive expiration. The outlet to the air chamber of the spirometer is through an iron pipe, 1 inch inside diameter. Attached to this pipe is a three way steam valve, one outlet of which is connected with a rubber mouthpiece.

The subject is comfortably seated before the spirometer and the nose closed with a clip. He inserts the mouthpiece into the mouth and breathes room air normally for from twenty to thirty seconds,

6. Pearce, R. G.: Am. J. Physiol. **43**:73, 1917.
7. Henderson, Y., and Prince, M.: J. Biol. Chem. **33**:325, 1918.

through one outlet of the valve.   Just at the height of a normal inspiration he is told to blow, the valve is suddenly turned so that all the expired air passes into the spirometer.   When the forced expiration is completed the valve is again turned, thus closing off the spirometer. A sample of this air is now drawn off and analyzed for carbon dioxid.   During this analysis the subject removes the nose clip and mouthpiece and breathes naturally.   After a few minutes the mouthpiece is again taken and room air is respired through the valve outlet. At the height of a normal inspiration the subject is told to blow but this time he expires into the room.   At the end of the deepest possible expiration he raises his finger as a signal, the valve is suddenly turned, and the contents of the spirometer is inspired.   This is held ten seconds and forcibly expired back into the spirometer.   A carbon dioxid analysis of this expired air is then made.   This procedure of inspiring the contents of the spirometer—holding ten seconds and expelling— is repeated until the carbon dioxid percentage of the expired air reaches a constant level.

The same technic is used to determine the rapidity with which a high concentration of carbon dioxid (from 12 to 13 per cent.) reaches the level of carbon dioxid in the venous blood.   In this case a carbon dioxid-rich air mixture is first put into the spirometer, the total volume equal to that which the subject forcibly expires after a normal inspiration.   The rebreathings, as described above, are performed until a constant carbon dioxid percentage is reached in the expired air.

TABLE 5.—THE RISE IN CARBON DIOXID FROM INTERMITTENT REBREATHINGS IN TWO NORMAL PERSONS AND TWO PATIENTS WITH EMPHYSEMA
Temperature, 20 C.   Barometer, 742 Mm. Hg.

Number of Intermittent Rebreathings	Percentage of Carbon Dioxid in Expired Air			
	Normal Subject	Normal Subject	Emphysema, Eli B.	Emphysema, Peter W.
1*..........................	4.88	4.48	5.40	6.08
2..........................	6.40	6.0	7.52	7.52
3..........................	7.04	7.20	8.28	8.80
4..........................	7.08	7.28	8.92	9.23
5..........................	7.28	7.26	9.16	9.50
6..........................	7.20	7.28	9.22	9.45
7..........................	7.28	7.28	9.40	9.50
8..........................	....	....	....	....

* The first analysis in each subject is the carbon dioxid content of a forced expiration after a normal inspiration of room air.

Table 5 contains the experimental data obtained in two normal individuals and two emphysematous subjects (Eli B. and Peter W.). Tables 6 and 7 show the results of taking a high percentage of carbon dioxid into the lungs and rebreathing until an equilibrium is attained. Curves plotted from these data are shown in Figure 3.

The data obtained show that, after four or five rebreathings, the carbon dioxid in the inspired air comes practically to a constant level and this occurs when a low as well as a high concentration is first taken into the lungs. Although the number of patients studied is too small to draw definite conclusions, yet the results seem to indicate that the tonometric function of the emphysematous lung is not seriously impaired. That is, under the experimental conditions, carbon dioxid equilibrium is reached between blood and lung air in approximately the same time in the emphysematous subject as in normal persons.

TABLE 6.—THE FALL IN CARBON DIOXID FROM INTERMITTENT BREATHING IN
TWO NORMAL PERSONS

Temperature, 20 C.   Barometer, 742 Mm. Hg.

Number of Intermittent Rebreathings (Spirometer Filled With 12.8 per Cent. Carbon Dioxid)	Percentage of Carbon Dioxid in Expired Air	
	Normal Subject	Normal Subject
1*	10.0	9.20
2	8.6	8.00
3	7.68	7.60
4	7.20	7.28
5	7.28	7.20
6	7.28	7.28
7	7.20	7.20

* The carbon dioxid content of the air forcibly expired after first filling the lungs with air containing 12.8 per cent. carbon dioxid and holding for ten seconds.

TABLE 7.—THE FALL IN CARBON DIOXID FROM INTERMITTENT REBREATHING
IN A PATIENT WITH EMPHYSEMA

Temperature, 22 C.   Barometer, 738 Mm. Hg.

Number of Intermittent Rebreathings (Spirometer Filled with 13 per Cent. Carbon Dioxid)	Percentage of Carbon Dioxid in Expired Air
	Emphysema, Eli B.
1*	10.24
2	9.72
3	9.50
4	9.56
5	9.56
6	9.45
7	9.45

* The carbon dioxid content of the air forcibly expired after first filling the lungs with air containing 13 per cent. carbon dioxid and holding for ten seconds.

It is apparent that such observations throw little light on the facility with which carbon dioxid can be eliminated from the body, because such important factors as the blood flow through the lungs, the available alveolar surface, and the efficiency of alveolar ventilation are not considered. The level at which carbon dioxid equilibrium is established is definitely higher in emphysema than in the normal.

Observations on several normal persons at rest have shown that the venous carbon dioxid as determined by the technic described above, varies between 7 and 7.4 per cent. at 20 C. and the prevailing barometric

pressure, 740 mm. Hg. Under similar experimental conditions the results have been consistently high in both Eli B. and Peter W. A few determinations of the alveolar carbon dioxid on these patients have also been high. Such abnormally high figures admit of two interpretations.

The carbon dioxid content of the venous and arterial pulmonary air (Y. Henderson) as estimated either does or does not represent the level of free carbon dioxid in the pulmonary venous and arterial blood respectively. There is little in favor of the negative side of the
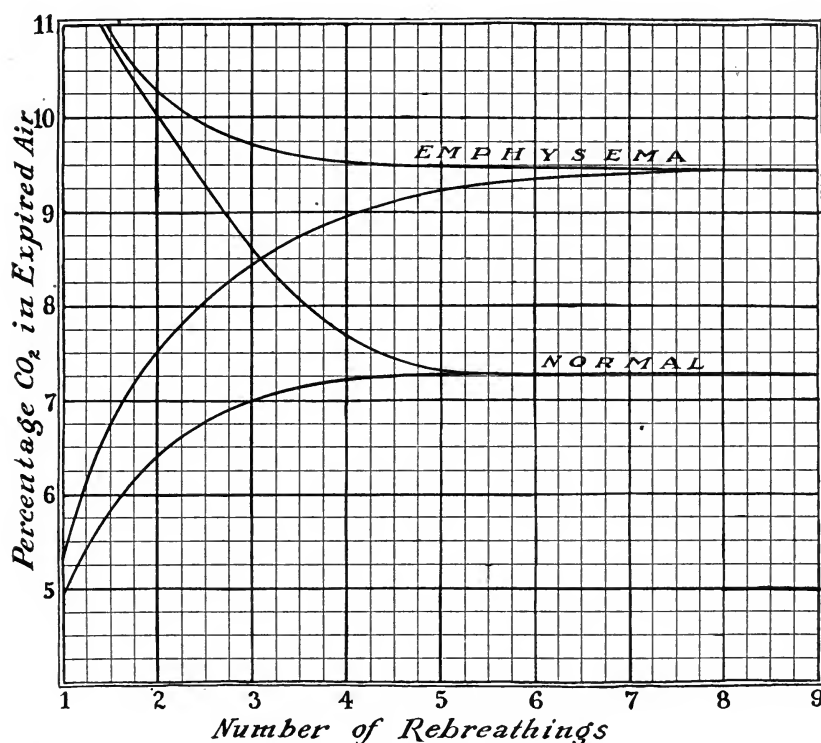
Fig. 3.—Curves plotted from experimental data to show the level at which equilibrium is established between the carbon dioxid of the lung air and the carbon dioxid tension of the venous blood in the normal and emphysematous subjects.

question unless one assumes that the methods for obtaining samples of the lung air are unreliable. On the other hand, as pointed out by Bohr, and particularly by Krogh,[8] the diffusion constant (the diffusion at 1 mm. tension difference during 1 minute, in cm. at 0 degrees 760 mm.) for carbon dioxid is such as to render the tension of this gas the same on the two sides of the pulmonary membrane. To study

8. Krogh, A.: Skand. Arch. f. Physiol. **23**:248, 1910.

this question, H-ion concentration (p_H) and total carbonate determinations were made on the arterial and venous bloods of the emphysematous subjects. The data from the bloods of normal persons at rest served as controls.

The arterial blood was obtained by direct puncture of the radial artery, using a similar technic as that employed by Stadie.[9] The venous blood was collected without stasis from one of the large veins at the bend of the elbow. Both samples of blood were delivered under oil into paraffin coated centrifuge tubes and immediately centrifuged at high speed. A little oxalate was added to prevent clotting. One c.c. of the separated plasma was delivered under carbon dioxid free ammonia water in the receiving cup of the Van Slyke apparatus and the total carbon dioxid content determined directly. This direct method appears to have certain advantages over the widely used technic of first exposing the plasma routinely to 5.5 per cent. carbon dioxid and determining the carbon dioxid combining power. It is simpler and with care taken to prevent the loss of carbon dioxid it gives results obviously more representative of the carbon dioxid content of the circulating blood particularly when one is dealing with pathologic conditions. Reference to and the data obtained in normal and pathologic individuals by the use of this direct method were presented in a preliminary report.[10] Recently Van Slyke and Stadie [11] have recommended its adoption.

TABLE 8.—TOTAL CARBONATE CONTENT OF THE ARTERIAL AND VENOUS PLASMA AND PH OF THE WHOLE BLOOD (ARTERIAL) IN FIVE NORMAL SUBJECTS AND TWO WITH EMPHYSEMA

Normal Individuals			Emphysema*		
Carbon Dioxid Reduced to 0 C. 760 Mm. in 100 C.c. Plasma		P_H Arterial Blood	Carbon Dioxid Reduced to 0 C. 760 Mm. in 100 C.c. Plasma		P_H Arterial Blood
Arterial, C.c.	Venous, C.c.		Arterial, C.c.	Venous, C.c.	
57.8	64.4	7.35	76.1	82.7	7.4
59.1	67.2	7.4	74.1	78.4	7.4
57.5	61.5	7.4	80.2	88.4	7.45
51.5	59.9	7.35	74.5	80.2	7.35
53.4	60.0	7.40	71.0	76.0	7.4

* Determinations made on different dates over a period of several months.

Table 8 contains the data for the total carbon dioxid content of the arterial and venous plasma along with the p_H of the whole arterial blood as drawn. The results on five normal individuals at rest are given to compare with similar data obtained at different dates on Eli B., and Peter W.

9. Stadie, W. C.: J. Exper. Med. **40**:215, 1919.
10. Scott, R. W.: Proc. Soc. Exper. Biol. & Med. **17**:18, 1919.
11. Van Slyke, D. D., and Stadie, W. C.: J. Biol. Chem. **41**:191, 1920.

It is seen that the total carbonate content of both the arterial and venous plasma in emphysema is distinctly above normal, while the H-ion concentration (p_H) of the whole blood as drawn is not appreciably changed. Only one interpretation can be placed on such results in view of the well established relation between the free and combined carbon dioxid to the H-ion concentration in blood. Associated with a high carbonic acid content there is a corresponding increase in the sodium bicarbonate so that the ratio $\dfrac{H_2CO_3}{NaHCO_3}$ and hence the H-ion concentration is maintained at appreciably a normal level.

DISCUSSION

It is clear from the data presented that a subject with chronic pulmonary emphysema will inspire relatively high percentages of carbon dioxid for several minutes with only small increases in the minute volume over that at room air. In interpreting this, attention must first be directed to the question of whether or not the carbon dioxid taken into the lungs under the experimental conditions, actually caused a retention of metabolic carbon dioxid. From the physical laws of diffusion there must be a slight pressure gradient from the blood to the lung air. If the carbon dioxid tension in the lungs is elevated, as was done in the foregoing experiments, the metabolic carbon dioxid is retained in direct proportion to this elevation. The data indicates this to be the case in emphysema as well as in the normal. There are, of course, variations in individual experiments, but, as a rule, increasing percentages of carbon dioxid in the inspired air cause a progressive drop in the metabolic output.

When this fact was first obtained it seemed quite paradoxical to assume that the subjects with emphysema possessed an increased tolerance to carbon dioxid particularly in view of the fact that they were distressed with slight exercise. Later, experiments were conducted to test the tolerance limit, when it was found that there was a fairly definite concentration at which the subject developed acute symptoms such as headache, nausea, dizziness, etc. Further study of this point indicated that the "break" in emphysema depended on two factors, i. e., the concentration of the inspired carbon dioxid and the length of the breathing period. For example, Peter W. developed acute distress in ten minutes breathing 11.4 per cent. carbon dioxid. A similar "break," although not so sharp, occurred while breathing 6.8 per cent. carbon dioxid for twenty minutes. An attempt was made to find a definite inverse ratio between inspired carbon dioxid and time of inhalation by having the subject inspire various concentrations until symptoms of intolerance developed. The results showed clearly, as would be expected, that as the percentage of inspired carbon dioxid

was elevated the time required to produce signs of intolerance diminished, but no definite constant (carbon dioxid inspired multiplied by length of breathing period) was obtained. The failure to obtain such a constant was due in part to the difficulty of recognizing the "break" with low concentration, particularly in the longer experiments, since it is necessary to depend on the patient's subjective sensations.

It is apparent from the foregoing that the length of the breathing period must be kept reasonably constant in contrasting the normal with the emphysema. However, when this factor is controlled, comparison of the data shows a sluggish response in the case of emphysema (Fig. 2). Two possibilities are suggested for this: (1) an increased capacity for storage of carbon dioxid in the body fluids; (2) a change in the sensitivity of the respiratory center. It is conceivable that the functional activity of the respiratory center may be depressed in emphysema through a slow process of adaptation. Observations bearing on this phase of the subject are under way but sufficient facts are not at present available to warrant any definite conclusions.

Evidence suggesting an increased capacity for binding carbon dioxid is afforded by the high level of blood bicarbonate (Table 8). As the buffer value of body fluids is proportional to the bicarbonate content, it appears that up to a certain limit, the emphysema subject can bind more carbon dioxid than the normal. Consequently, higher percentages of the gas may be inspired before a change occurs in the H-ion concentration in the blood of sufficient magnitude to stimulate the respiratory center. This seems to account in part for the sluggish respiratory reaction observed.

The fact that the addition of carbon dioxid to blood raises not only the carbonic acid, but also the sodium bicarbonate content was first recognized by Zuntz. Later Gürber studied the question and concluded that carbon dioxid caused a passage of chlorids from the plasma into the corpuscles. Recently Fridericia [12] confirmed the work of other investigators by showing that as the carbon dioxid tension of blood is elevated, the carbon dioxid combining power of the plasma and the red cells is also raised. His results indicate further that the increased carbon dioxid combining power of the plasma is due chiefly to the passage of chlorid ions from the plasma into the corpuscles. The sodium thus liberated in the plasma combines with carbon dioxid to form more bicarbonate.

Experimental proof that the blood bicarbonate was elevated was obtained by me [13] in cats made to breathe varying concentrations of

12. Fridericia, L. S.: J. Biol. Chem. **42**:245, 1920.
13. Scott, R. W.: Am. J. Physiol. **44**:196, 1917.

carbon dioxid. This was later confirmed by Henderson and Haggard [14] On the other hand, there is much experimental and clinical evidence to show that the blood bicarbonate is diminished when acids other than carbon dioxid are added to the blood. It is clear, therefore, that the tissue carbonate is no fixed quantity, but may undergo wide variations, the H-ion concentration being maintained within normal limits. This was recently emphasized by Henderson and Haggard.[15] They showed from animal experiments that there were four theoretical alterations in the normal free and combined carbon dioxid content of the blood. One of these, in which carbonic acid and sodium bicarbonate are both at a high level but the normal ratio is apparently maintained, is illustrated in emphysema. The progressive degenerative process in the lungs in this condition causes an increasing impediment to alveolar ventilation, with the consequent interference with gaseous exchange. This ultimately leads to a retention of carbon dioxid as well as a certain amount of chronic anoxemia. The high level of free carbon dioxid of the blood in emphysema is attained gradually so that ample time is afforded for the development of compensatory mechanisms. The maintenance of the body bicarbonate at a permanent high level appears as one important illustration. This enables the emphysematous subject to tolerate a high carbon dioxid tension in the blood normally and also affords a certain protection against undue fluctuations in H-ion concentration which might otherwise occur from metabolism. Considering the body bicarbonate as a chemical factor of safety, it appears that the emphysema subject can tolerate for short periods higher concentrations of inspired carbon dioxid than the normal. When, however, the tissue buffer is exceeded, there is little mechanical factor of safety as represented by pulmonary ventilation and acute distress develops suddenly. The normal subject on the other hand has a considerable pulmonary reserve and compensates for carbon dioxid retention by increasing ventilation. Consequently no sudden "break" occurs but discomfort develops gradually.

SUMMARY

1. Two patients with chronic pulmonary emphysema of the socalled "large lunged" type have been studied over a period of several months and compared with normal persons as controls.

2. It was found that the emphysematous patients breathed high percentages of carbon dioxid (from 8 to 10 per cent.) for ten and fifteen minute periods with relatively little increase in the minute volume, and without subjective symptoms of distress. Slightly higher

14. Henderson, Y., and Haggard, H. W.: J. Biol. Chem. **33**:343, 1917.
15. Henderson, Y., and Haggard, H. W.: J. Biol. Chem. **39**:163, 1919.

percentages were intolerable and caused a sharp "break" with symptoms of acute distress such as headache, nausea and dizziness. The concentration of inspired carbon dioxid necessary to produce signs of intolerance was found to vary inversely with the length of the breathing period.

3. There was a definite elevation in the free and combined carbon dioxid of the blood in emphysema, but the ratio $\dfrac{H_2CO_3}{NaHCO_3}$ was such as to maintain the H-ion concentration within normal limits.

4. It is suggested that the increased buffer of the body fluid in emphysema compensates to some extent for the impairment of pulmonary ventilation and offers a certain protection against undue fluctuations in H-ion concentrations which might otherwise occur.

OBSERVATIONS ON THE CHEMICAL PATHOLOGY OF THE BLOOD IN PERNICIOUS ANEMIA AND OTHER SEVERE ANEMIAS *

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OMAHA

INTRODUCTION

This study is confined to fundamental chemical conditions of the blood in pernicious and severe secondary anemia and, for comparison, to a study of the same conditions in one series of normal subjects and in another series of pathologic conditions other than anemias. We found early in our study that the total blood solids in clearly diagnosed cases of pernicious anemia were extraordinarily low. From the comparison series above mentioned it appeared that so great an abnormal deviation is so uncommon an occurrence in other pathologic conditions as to make extremely low blood solids one of the pathologic characteristics of pernicious anemia and severe secondary anemia. Further observation showed marked deviation from normal values in the total nitrogen of the whole blood in this condition but a much less pronounced deviation in the total nitrogen of the plasma. However, on studying the ratio of the whole blood nitrogen to the total nitrogen of the plasma a relation ("index" in column 7 of Tables 1, 2 and 3) appeared that is also a pathologic characteristic of severe anemia. There is reason to believe that this abnormal index and the excessively low blood solids are as constantly associated chemical conditions of severe anemias as the low red cell count is characteristic of the morphology of this blood. We regard the present study as introductory and we are making further observations on these conditions.

METHODS

The methods used were an application of the principles developed in a previous publication [1] but some deviations from the technic there described and some corrections were made. There is also added the following method for the determination of total plasma nitrogen, which obviates the difficulty of separating such small amounts of plasma as are here used, from corpuscles. The technic for blood solids was used as described.[1]

For whole blood and plasma nitrogen the blood was collected in one weighed and stoppered test tube containing exactly 12 c.c. of fluorid-salt solution of the following composition: sodium fluorid, 3.5 gm.; sodium chlorid, 5.0 gm. per 1,000 c.c. distilled water. The alkalinity to phenolphthalein of 1,000 c.c. or more should be neutralized by adding concentrated hydrochloric acid, one drop at a time, until a test remains colorless with the indicator. Enough of the 10 per cent. sodium hydroxid used elsewhere in these methods should then be added drop by drop from the buret to just restore the alkalinity to phenolphthalein as found on a test sample of the medium. Without the precaution of regulating the reaction of the fluorid-salt medium the results obtained for plasma nitrogen might be vitiated entirely by solution or extraction of corpuscles. The first two drops of finger blood and no subsequent ones, were received in the previously described test tube which was then reweighed to ascertain by difference the weight of the blood. From this total volume two aliquots of 2 c.c. each, designated A 1 and A 2, respectively, were removed for the determination of the total nitrogen of the whole blood. Care should be taken to mix thoroughly the contents before each aliquot is taken in order to avoid error from partial sedimentation of corpuscles, which occurs rapidly. The remaining volume is transferred to a conical centrifuge tube and centrifuged thirty minutes. The clear and nearly always colorless liquid is decanted from the corpuscles into another tube from which 5 c.c., designated as AA, is removed for the determination of the total nitrogen of the plasma. This 5 c.c. is, of course, an aliquot of the original volume.

The two drops of blood usually weigh from 50 to 70 mg., and the total volume of the original blood dilution may be taken at e. g. $V = 12.07$ c.c., from which aliquots of 2./12.07 and 5./12.07 have been taken of the weight of the two drops of blood.

If a nonprotein determination is also desired, the ten or more drops of finger blood next following the first two are received in about 10 c.c. of distilled water (not in sodium fluorid solution as directed in the previous publication [1]) and this is designated as B. The tube for total solids being designated as C, an entire set of determinations consist of A 1, A 2, AA, B and C. The nitrogen in A 1, A 2 and AA is determined as previously described [1] except as the following modifications have much improved the process.

All neutralized unknown solutions that are to be nesslerized are first made to a volume of 40 c.c. in a 100 c.c. cylinder, from which the liquid is delivered into 10 c.c. of the below described Nessler solution, which has been measured with a volumetric pipet into a carbon dioxid flask. The final volume is thus 50 c.c. without further

measurement or transfer and the Nessler reaction always occurs under comparable conditions of concentration. When a series of determinations is to be made it is advantageous to let the several cylinders, each made to a volume of 40 c.c., stand in a row, with carbon dioxid flask with the measured 10 c.c. of Nessler standing beside each, until the operator is ready to do the whole series of nesslerizations and colorimetric readings in order.

The modified Nessler reagent is made by mixing 200 c.c. of the Folin[2] potassium-mercuric iodid stock solution with 100 c.c. of 10 per cent. sodium hydroxid and 200 c.c. of distilled water. With this modification the progressive change in color immediately after mixing as above is less rapid. By making the colorimetric reading against the permanent color standard, in the interval between four and seven minutes after mixing, the agreement between duplicates on the same reagents can be kept within a few tenths of a millimeter. Duplicates on blood also show exceedingly small deviations.

TABLE 1.—Normal Human Blood

1 Blood No.	2 Subject No.	3 Date	4 Solids, per Cent.	5 Whole Blood N, per Cent.	6 Plasma N, per Cent.	7 Index Whole Blood N % / Plasma N %
1	1	10/ 7/19	20.6	3.16		
2	1	10/27/19	20.3	3.48	0.74	4.7
3	1	11/11/19	20.8	3.00	0.66	4.5
38	1	12/24/19	....	3.34	0.60	5.6
42	1	5/ 6/20	....	2.78	0.81	3.4
45	2	6/ 1/20	....	3.18	0.88	3.6
46	2	6/ 4/20	....	3.29	0.82	4.0
47	2	6/29/20	....	2.88	0.83	3.5
59	2	7/ 2/20	20.4	2.83	0.96	2.9
60	2	7/13/20	....	3.26	0.78	4.2
48	3	6/ 3/20	....	3.33	1.05	3.2
49	3	6/ 9/20	....	3.36	1.14	2.9
50	3	6/25/20	22.6	2.73	1.03	2.7
51	3	6/30/20	....	2.90	0.92	3.2
57	3	7/ 2/20	19.1	2.73		
58	3	7/ 2/20	....	2.84	1.08	2.6
61	3	7/10/20	22.4	2.65	1.06	2.5
62	3	7/13/20	18.8	2.85	0.85	3.4
52	4	6/ 8/20	....	3.22	1.06	3.0
53	4	6/25/20	22.8	3.14	0.82	3.8
54	4	6/30/20	20.8	2.94	0.92	3.2
55	5	6/16/20	....	3.15	1.13	2.8
Average index...						3.5

The same stock quantity of distilled water and the same stock of reagents should be used throughout a given series of determinations that are to be calculated by means of a given base value (0.35 mg. N). It is well worth noting from the standpoint of accuracy in dealing with such small amounts of nitrogen as are used that this base value always functions as a blank on the reagents, including the distilled water, as well as being the base of calculation.

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2. Folin, O., and Dennis, W.: Nitrogen Determination by Direct Nesslerization. I. Total Nitrogen in Urine, J. Biol. Chem. **26**:479, 1916. Folin, O., and Hsien, Wu: A System of Blood Analysis, J. Biol. Chem. **38**:89, 1919.

Pebbles or other means to prevent bumping during the digestions have been found unnecessary except for nonprotein nitrogen.

The value of R used in the calculation of the colorimetric reading into mg. of nitrogen was determined for each series of unknowns by comparing the results of a single test each on 0.35 mg. and 0.15 mg. standard nitrogen.

With the above modifications we have found the use of a single constant color standard, which is the special characteristic of this method, not only accurate as previously described, but also quite expeditious when many determinations were to be made as in these experiments. This is due to the elimination of the time and labor consumed in the customary procedure of making a fresh standard for each and every determination.

TABLE 2.—BLOOD IN PERNICIOUS ANEMIA AND IN SECONDARY ANEMIA

1 Blood No.	2 Case No.	3 Date	4 Solids, per Cent.	5 Whole Blood N, per Cent.	6 Plasma N, per Cent.	7 Index = Whole Blood N % Plasma N %	8 Diagnosis
15	1	10/ 9/19	13.0	2.34			
16	1	10/11/19	12.7	1.77	1.14	1.6	Pernicious anemia
17	1	10/18/19	13.2	2.10	1.19	1.8	and syphilis
18	1	10/29/19	12.0	2.12	1.25	1.7	
19	2	11/ 1/19	12.6	1.99	0.99	2.0	
20	2	11/ 4/19	12.6	2.03	0.82	2.5	Chronic secondary
21	2	11/ 6/19	13.5	1.97	1.05	1.9	anemia
35	3	12/ 9/19	8.0	1.34	0.90	1.5	
36	3	12/11/19	9.8	1.43	0.73	2.0	
39	3	12/27/19	10.1	1.29	0.76	1.7	Pernicious anemia
44	3	5/20/20	....	2.00			
65	3	7/17/20	14.7	2.17	1.09	2.7	
23	4	11/18/19	14.5	2.70	0.97	2.8	Pernicious anemia
40	5	4/27/20	....	1.38	1.01	1.4	Pernicious anemia
41	6	4/30/20	9.0	2.16	1.02	2.1	Secondary anemia
63	7	7/16/20	12.3	2.25	0.74	3.0	Exophthalmic goiter and sec. anemia
66	8	7/21/20	13.6	2.37	1.04	2.2	Suspected pernicious anemia
Average index....................................						2.1	

CLINICAL DATA ON CASES IN TABLE 2

The clinical data recorded below were primarily intended to present only the salient pathologic conditions that might stand in relation to the factor of anemia. We, however, doubt that such a selection is justifiable in view of the possible interrelations of all pathologic conditions in the same subject. We have, nevertheless, selected the trio of conditions that are commonly regarded as constituting the essentials of the syndrome of pernicious anemia, i. e., the blood count, the gastro-intestinal-abdominal findings and the neurologic factor. These include the low red cell count, the achlorhydria, and the evidences of cord degeneration, all of which, it should be remembered, need not be concurrent, especially the cord symptoms. After having

made this selection, and after some reflection on what might be the consequences of the conditions revealed by the laboratory findings, we were much impressed by the almost constant finding, in the physical examination, of more or less pronounced edema in nearly all these anemia cases whether pernicious or secondary. Minor functional but not organic cardiac symptoms and a palpable liver and spleen were practically constant concomitants of the edemas. Whether these edemas are to be regarded as primarily due to mechanical, obstructive factors or to chemical alterations of blood composition or of vascular endothelium is not answered by our present study

TABLE 3.—HUMAN BLOOD IN PATHOLOGIC CONDITIONS (OTHER THAN PERNICIOUS ANEMIA)

1 Blood No.	2 Case No.	3 Date	4 Solids, per Cent.	5 Whole Blood N, per Cent.	6 Plasma N, per Cent.	7 Index Whole Blood N % / Plasma N %
13	1	11/15/19	....	1.29	0.71	1.5
14	2	11/13/19	19.3	3.21	0.80	4.0
26	3	12/11/19	16.0	2.74	0.67	4.1
4	4	9/30/19	18.4	2.71		
5	4	10/ 7/19	18.0	2.27		
6	4	10/16/19	18.9	2.78	0.83	3.4
7	4	10/24/19	18.8	3.15	0.62	5.1
8	5	10/ 2/19	18.0	2.75		
9	5	10/ 3/19	18.8	2.74		
10	5	10/14/19	18.8	2.80	0.81	3.5
11	5	10/22/19	19.3	3.12	0.98	3.2
12	6	10/29/19	15.7	2.31	0.64	3.6
31	7	12/16/19	20.9	3.30	0.66	5.0
37	7	12/18/19	19.0	2.63	0.65	4.0
24	8	11/20/19	20.4	2.91	0.76	4.0
43	9	5/20/20	18.4	3.13		
56	10	7/ 9/20	17.5	2.70	0.64	4.2
Average index......						3.8

All hemoglobin determinations were made according to Sahli.

Differential blood counts were used in making the diagnosis of pernicious anemia.

REPORT OF CASES

CASE 1.—Male, half Indian, half Mexican, aged 40.
Diagnosis.—Pernicious anemia and syphilis.
Blood Counts:

Date 1919	Hemoglobin, Per Cent.	Red Blood Cells	Leukocytes
June 5..............	20	800,000	4,600
June 6..............	18	770,000	2.950
June 18..............	20	870,000	6,500
June 26..............	19	830,000	4,500
July 8..............	36	1,460,000	2,600
July 21..............	35	1,900,000	2,100
July 31..............	28	2,150,000	4,500
Aug. 26..............	46	2,600,000	3,700
Sept. 6..............	60	1,780,000	.....
Oct. 5..............	40	870,000	.....
Oct. 14..............	..	1,700,000	.....
Nov. 25..............	..	1,456,000	.....

Gastro-Intestinal and Abdominal Symptoms.—Epigastric pain; sour stomach; constipation; fluid in peritoneal cavity, moves to dependent portion, fluctuates; liver palpable three fingers' width below costal margin; hepatic region very tender.

Neurologic Symptoms.—Practically negative.

CASE 2.—Male, Mexican, aged 38.

Diagnosis.—Chronic secondary anemia.

Blood Counts:

Date 1919	Hemoglobin, Per Cent.	Red Blood Cells	Leukocytes
Oct. 30..............	50	1,640,000	7,700
Nov. 2..............	45	2,700,000	8,400
Nov. 7..............	45	2,200,000	8,100
Nov. 8..............	..	....	7,000
Nov. 20..............	55	2,464,000	15,500
Nov. 25..............	..	3,160,000	......

Gastro-Intestinal and Abdominal Symptoms.—Practically negative.

Neurologic Symptoms.—Negative.

CASE 3.—Male, American, aged 50.

Diagnosis.—Pernicious anemia.

Blood Counts:

Date 1919	Hemoglobin, Per Cent.	Red Blood Cells	Leukocytes
Dec. 6..............	20	530,000	2,900
Dec. 7..............	12	600,000	2,600
Dec. 11..............	9	405,000	2,300
Dec. 12..............	17	665,000	2,400
Dec. 13..............	17	900,000	1,600
Dec. 15..............	..	670,000	2,100
Dec. 18..............	15	520,000	2,400
Dec. 21..............	17	600,000	2,300
Dec. 30..............	11	600,000	5,300
1920			
May 7..............	35	1,270,000	3,000

Gastro-Intestinal and Abdominal Symptoms.—Pain, nausea, vomiting at times; constipation; tenderness in region of gallbladder; abdomen full and rounded, highly tympanitic; no fluid; liver above costal margin; spleen palpable.

Neurologic Symptoms.—Pain and twitching of legs and arms, numbness; progressive weakness until unable to stand or walk; knee jerks exaggerated; ankle clonus present; Babinski positive.

CASE 4.—Female, German, aged 40.

Diagnosis.—Pernicious anemia.

CASE 5.—Female, American, aged 32.

Diagnosis.—Pernicious anemia.

Blood Counts:

Date 1920	Hemoglobin, Per Cent.	Red Blood Cells	Leukocytes
April 13..............	15	640,000	6,000
April 15..............	20	710,000	5,000
April 25..............	15	680,000	4,200
May 7..............	25	980,000	3,400

Gastro-Intestinal and Abdominal Symptoms.—Pain and bloating; abdomen very tender; constipation; achlorhydria; mass extending from epigastrium below right costal border, apparently the liver; spleen palpable about 1 inch below costal margin.

Neurologic Symptoms.—Practically negative.

CASE 6.—Male, American, aged 39.

Diagnosis.—Secondary anemia.

Blood Counts:

Date 1920	Hemoglobin, Per Cent.	Red Blood Cells	Leukocytes
April 22..............	32	2,800,000	5,000
May 4..............	38	3,180,000	.....

Gastro-Intestinal and Abdominal Symptoms.—Practically negative.

Neurologic Symptoms.—Practically negative.

CASE 7.—Female, American, aged 37.

Diagnosis.—Exophthalmic goiter; secondary anemia.

Blood Count:

Date 1920	Hemoglobin, Per Cent.	Red Blood Cells	Leukocytes
July 1...............	60	3,200,000	4,600

Gastro-Intestinal and Abdominal Symptoms.—Appetite poor; diarrhea; free hydrochloric acid. Abdomen: no masses; no rigidity; no tenderness; liver enlarged, palpable 2 cm. below costal margin; spleen enlarged, palpable.

Neurologic Symptoms.—Dizziness; nervousness; insomnia.

DISCUSSION OF RESULTS

A comparison of Columns 4 in the three tables shows that an extreme decrease in the total solids of the whole blood is one of the prominent characteristics of a severe anemia. The normal values as shown by Table 1 may be taken to range approximately from 19 to 22 per cent. and similar or slightly lower values are found in hospital cases other than severe anemias as shown by Table 3. These latter data are of importance in showing that it is the anemia and not other possible metabolic derangement that is responsible for the low values of Table 2. These values in pernicious anemia are so low that if they represented only or principally change in chemical composition of the blood we should expect fatal physiologic consequences. Evidently, it is the outstanding characteristic alteration of severe anemia—the decrease in the number of red corpuscles—that is responsible for the low value of the total solids. A study of the clinical data confirms this proposition. We should, however, note carefully that the possibility of considerable change in the chemical composition of the blood is not to be excluded from the conditions which prevail in severe anemia. We shall report further on these and related questions in the near future.

We then have in the diminution of total solids a chemical representation of that characteristic of anemia which has heretofore been represented only by morphologic data, i. e., the red cell count.

A comparison of Columns 5 in the three tables shows that the total nitrogen of the whole blood comports itself similarly to the total solids, showing very low values for pernicious and severe secondary anemias. In this respect also the values of Table 3 for other pathologic conditions show more deviation from the normal level of Table 1 than the solids showed. This might be expected from the almost universal presence of the anemic factor in practically all pathologic conditions. A comparison of the clinical data leads us here also to attribute the decrease in nitrogen content primarily and principally but not wholly to the low red cell count. The question is very justly raised here whether part of this result may not be due to decrease in plasma nitrogen as well as to diminished number of red corpuscles. That changes in the albumin and globulin content either absolute or relative should occur in severe anemia is both possible and probable. However, the results shown by Columns 6 of the three tables fail to show a decrease in the plasma nitrogen whether the subjects be anemic or otherwise affected. On the contrary, if the plasma nitrogen undergoes any change in the pathologic conditions represented it is in the direction of increased concentration of nitrogen. We may, with some justice, attribute this tendency to the retention of waste nitrogenous products or to altered osmotic equilibria, both of which probably occur in most pathologic conditions. Provisionally, until we have made further investigations, we believe it to be a plausible proposition that the plasma interposes, for physiologic reasons, great resistance to a diminution in its nitrogen concentration, and we believe that plasma nitrogen concentrations that approach 1 per cent. are pathologic. In this connection it should be noted that the reaction of the collection medium from which the corpuscles are centrifuged should be controlled carefully, either as previously described or otherwise, in order to avoid erroneously high results for the plasma nitrogen due to solution of some corpuscles or to extraction of nitrogenous substances from the corpuscles between the time of collection and that of decantation.

We have, then, in the whole blood nitrogen, as well as in the solids, a chemical representation of the morphologic characteristic of low red cell count. We have tested experimentally on various physiologic and pathologic conditions in human subjects the reliability of this chemical expression for anemic conditions with (unpublished) results that are fully confirmatory.

It is now possible to study the quantitative relations between the whole blood nitrogen and the plasma nitrogen since the direction

of variation of each is known. When the whole blood nitrogen undergoes pathologic change it always decreases in anemia, and we have seen that the plasma nitrogen either holds its normal value or increases. The direction variation is such that the ratio $\frac{\text{Whole Blood N, }\%}{\text{Plasma N, }\%}$ under pathologic conditions diminishes since the numerator decreases and the denominator increases or remains constant. This ratio we will call nitrogen index and it is clear that as an anemia becomes more severe this index becomes smaller. The three tables adequately show how well this index expresses these pathologic conditions as well as physiologic normality.

SUMMARY

1. Human blood from three series of persons has been examined for its concentration in (a) total solids, (b) total nitrogen in whole blood, (c) total nitrogen in plasma. The first series comprised physiologically normal persons, the second cases of pernicious anemia and severe secondary anemia, the third cases of various pathologic conditions other than severe anemia.

2. A method has been described for the determination of plasma nitrogen in very small amounts of blood whereby plasma and corpuscles are separated after dilution.

3. The total solids of the blood of pernicious anemia and also of severe secondary anemia show great decrease from normal values or even from that of other chronic hospital cases. This decrease is due primarily to the large diminution in number of the red corpuscles and only in minor degree to decrease in plasma solids.

4. The total nitrogen of the whole blood in pernicious anemia and also in severe secondary anemias shows, like the total solids, a great decrease from the normal values. The principal cause here also is diminution in the number of the red corpuscles.

5. The percentage of total solids and of whole blood nitrogen are the essential chemical correlates of the number of red corpuscles, i. e., there is a marked proportionality in these two independently determinable factors.

6. The total plasma nitrogen in contradistinction to the total blood nitrogen either maintains its normal limits of constancy or tends to increase in percentage above that of most normal bloods, but in any case it has no tendency to decrease its nitrogen value.

7. Since in all severe anemic conditions the whole blood nitrogen decreases while the plasma nitrogen tends to increase, the resultant ratio of the first to the second, which constitutes a nitrogen index, shows from the direction of variation in both factors a natural tendency to diminish in proportion to the severity of the anemia. This index may be used as an indicator of the state and progress of the anemic condition.

THE PATHOLOGY OF EPIDEMIC PNEUMONIA IN MICE AND GUINEA-PIGS *

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The subject of epidemic pneumonia has been receiving a great amount of attention since the recent epidemics of streptococcus pneumonia and influenzal pneumonia. There are still many unknown factors of pathogenicity, virulence, invasiveness and toxicity of micro-organisms which produce epidemic diseases. These terms commonly are used without clear distinction of meaning.[1] The difficulty of reproducing characteristic epidemic lesions or even causing infection in animals with cultures of highly specialized strains of bacteria is well known. In view of these difficulties in experimental reproduction of an epidemic disease, it has seemed possibly more profitable to study the natural processes of an animal epidemic of pneumonia, followed through its entire course of development and subsidence.

The opportunity to observe and study such an epidemic presented itself in the animal room of the U. S. Naval Hospital, Chelsea, Mass., during the late winter and early spring of 1919. Distemper and epidemic pneumonia in laboratory animals has been the subject of several valuable papers,[2] but these investigations have been directed primarily toward establishing the etiologic relationship of the *Bacillus bronchicepticus* to these diseases. Very good evidence has been presented that this bacillus is the causative micro-organism in certain common epidemics of distemper and pneumonia.

In order to interpret properly the origin and course of this animal epidemic, it is necessary to describe the location of the cages in the animal room and give the number of animals exposed to the infection. This room measured ten feet square and had three steel shelves for cages on each of two opposite sides. On one side there were only guinea-pig cages, three rows of four each. On the other side the two lower shelves held eight guinea-pig cages and the top shelf twelve mice cages. At the beginning of the epidemic there were about fifty guinea-pigs in stock. During the epidemic, three lots of a dozen each were received from outside stock, making a total of eighty-six pigs exposed to the infection. Of these it is estimated that twenty-five

1. Topley, W. W. C.: The spread of bacterial infection, Lancet **1**:1, 1919.
2. Ferry, N. S.: A preliminary report of the bacterial findings in canine distemper, Am. Vet. Rev. **37**:499, 1910.

developed recognizable symptoms of respiratory disease; a necropsy was performed on fifteen. The mice cages were crowded together, partly placed on top of one another, contained more mice than intended for their size, and were harder to keep clean than the guinea-pig cages. There were about 150 mice in these cages at the beginning and they were being increased rather rapidly by breeding. These factors probably favored the origin of the infection in the mice. Twenty-four mice with symptoms of respiratory infection were later subjected to necropsy. Several died during the early part of the epidemic and were not examined. Many others were noted with distinct or questionable illness and recovered. A conservative estimate of the total number observed sick would be fifty.

The infection in the mice at first had the characteristics of what is commonly called distemper in animals. The sick mice were identified by the affected appearance of their eyes, there being an excessive conjunctival secretion, somewhat purulent, with swollen partly closed lids and desquamation and depilation in the surrounding epithelium. Occasionally a nasal discharge and cough were noted. There also was some indisposition and roughening of the fur. Few died during this period and bacteriologic or pathologic examinations were not made. It seemed very probable, however, from these observations and the subsequent course, that the epidemic pneumonia took origin in this manner.

The first intimation of a bronchial infection among the mice occurred a few weeks after the distemper symptoms had been noted. There had been a continuation and increase of the distemper symptoms when it was observed that a number of the mice had distinctly abnormal respirations. The breathing was more rapid than normal, but most noticeable was its deep or labored character, with heaving sides and use of accessory muscles of respiration, the effort fairly shaking the animal. These mice otherwise did not appear particularly sick. Their fur was slightly roughened and they were gaunt, but they were quite active when disturbed and were feeding. Some of these mice were isolated for a time, did not die within a week or two, so were killed and examined.

The necropsies presented constantly a firm grayish white lobular consolidation in one or more lobes, most frequently the median and cephalic lobes, rarely the larger caudal lobes which usually were the seat of a compensatory emphysema. There was no pleurisy. On gross section the dilated bronchi could be seen distinctly and a thick purulent exudate expressed from the lumen. The walls of the bronchi were thickened by a firm grayish infiltration. The smaller lobes were completely involved. The larger lobes, particularly the large

caudal lobes, frequently presented a similar grayish peribronchial infiltration along the main bronchi near the hilus, the remainder of the lobe being emphysematous.

Microscopic examination of these lungs disclosed excellent examples of purulent bronchitis, or interstitial bronchopneumonia as defined by MacCallum [3] in postmeasles streptococcus bronchopneumonia. Various stages were found. Typically the bronchi were dilated and filled with a dense polymorphonuclear exudate (Fig. 1). The mucosa tended to be a thick hyperplastic layer with very thick and long cilia, but in some places was desquamated. The bronchial walls were greatly thickened by a dense infiltration of mononuclear cells of the lymphoid variety. The thickness varied with the duration and stage of the disease and the lobe examined. A striking feature in many sections was the mononuclear cell infiltration about blood vessels, of similar character to the peribronchial infiltration.

The terminal bronchioles in these cases frequently appeared to drain areas of dense polymorphonuclear alveolar exudate. It seemed possible that the main part of the polymorphonuclear exudate found farther along in the dilated bronchi might come from these alveolar lesions, the irritant features of which would give rise to the more chronic protective mononuclear peribronchial reaction. In many places, however, a distinct passage of polymorphonuclear cells through the bronchial mucosa could be seen.

The alveoli of these lungs presented variable conditions, in addition to the focal polymorphonuclear lesion at the terminal bronchioles. There was commonly a partial or complete atelectasis of the alveoli intervening between enlarged bronchi. The exudate within these alveoli consisted chiefly of sparse mononuclear cells, some containing pigment granules, an occasional polymorphonuclear leukocyte or finely granular albuminous material. In lobes in which there was only partial hilus bronchial involvement, the alveoli of adjacent uninvolved areas were markedly emphysematous.

Such cases of purulent bronchitis continued to occur among the mice for a few weeks, with occasional deaths after an illness of several days or weeks. Most of the distinctly sick mice were killed at selected periods and examined. As the infection progressed the areas of polymorphonuclear alveolar exudate increased and the mononuclear peribronchial infiltration decreased. Rather suddenly it was noticed that the type of the disease had changed. Instead of the prolonged illness with marked respiratory symptoms and few toxic symptoms, mice were found dead in cages where routine inspection

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3. MacCallum, W. G.: Pathology of pneumonia at a base hospital, J. A. M. A. **70**:1150 (April 20) 1918.

on the preceding day had not shown any affected mice. Closer inspection on succeeding days identified these fulminating cases by their inactiveness and their slow and somewhat irregular respirations.

Necropsies done on these mice with toxic symptoms and fulminating course, found dead or killed, presented constantly hemorrhagic lesions in the lungs. The hemorrhagic areas varied from a light red, mottled with air filled alveoli, to a solid very dark red color. The gross appearance was striking. The smaller and more dependent lobes
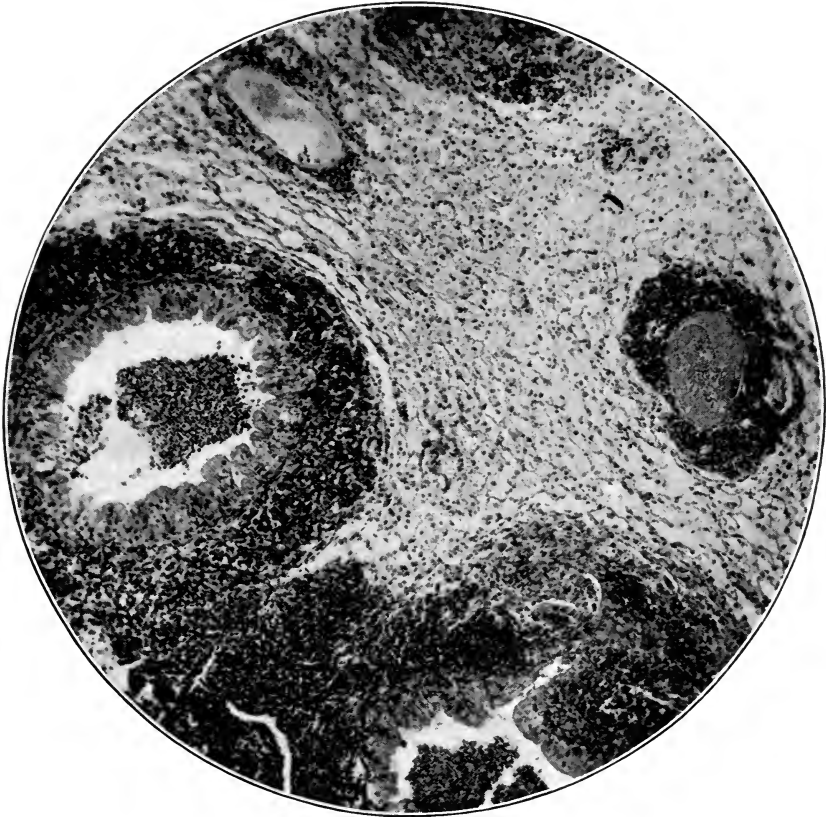
Fig. 1.—Microphotograph of a lung section from mouse 1, showing an advanced active purulent bronchitis. The bronchi are filled with polymorphonuclear leukocytes, the mucosa is hyperplastic and the wall densely infiltrated with mononuclear cells. There is a similar mononuclear perivascular infiltration. The alveoli are atelectatic, containing serum and a few mononuclear cells. Cultures gave a pure growth of the *Bacillus bronchisepticus.*

were most affected, the caudal lobes commonly being distinctly emphysematous and pink. Lobes which presented only a slight red mottling on the surface contained more extensive hemorrhagic areas in the center.

Microscopic sections of these hemorrhagic lungs presented a type of pneumonia rarely met, except in fulminating cases at the height of an epidemic of pneumonia. It is rare probably because it is a stage much earlier than is seen at necropsies of pneumonia of pneumococcus origin, or of low grade pneumonias of other origin. The lesion is a rather irregular central or lobular alveolar hemorrhage with numerous distended air spaces scattered throughout the area (Fig. 2).
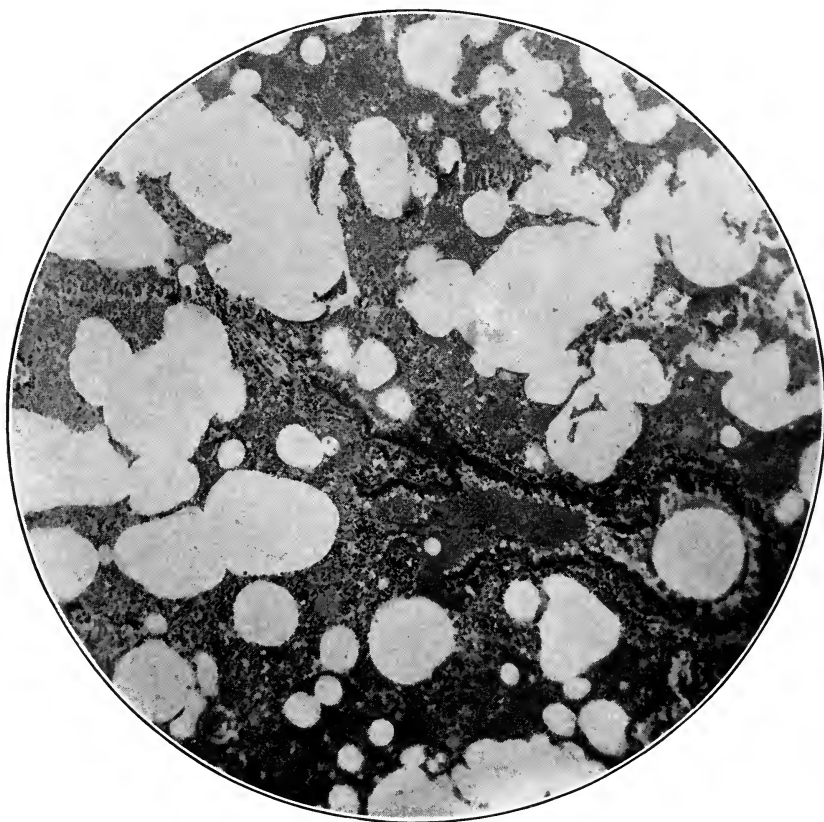

Fig. 2.—Microphotograph of a lung section from mouse 23, showing an emphysematous hemorrhagic type of pneumonia characteristic of the acute toxic stage of the epidemic.

Various stages of this were found. Some mice died at a very early period when no other lesion than an extreme capillary engorgement and serous alveolar exudation could be found, although usually in the central part of the lobes areas of alveolar hemorrhage were present.

The subsidence of the epidemic among the mice was prolonged and marked by a recrudescence of the acute toxic hemorrhagic form of the disease. Greater numbers of the sick mice began to have promi-

nent respiratory embarrassment and prolonged course. Such mice at necropsy presented a great variety of lesions in different lobes or even in the same lobe; purulent bronchitis in many stages of heal· ing with obliteration of bronchi, limited or widespread polymorphonuclear alveolar exudate, lobular or fused areas of alveolar hemorrhage or simple capillary engorgement.

The infection among the guinea-pigs appeared later than among the mice and apparently took origin from the prevailing mouse epidemic at about the height of the latter. It is recalled that there were two rows of guinea-pig cages below the mice cages on one side of the animal room. The first infected guinea-pigs were noted in the row directly beneath the mice, and the infection was limited to the pigs of this side of the room for two weeks. The spread to the other side of the room dated from a general cleaning and sterilization of the cages, isolation of all sick pigs and transfer of all healthy appearing pigs to common outdoor pens or to cleaned cages on the uninfected side of the room. This attempt to rid the animal room of all infected cages only served to spread the disease. This was understood later when it was found by many necropsies and cultures that in an infected stock many apparently normal pigs show some lung lesion and give positive cultures of the *Bacillus bronchisepticus* from the trachea in more than 50 per cent.

PROTOCOLS

The symptoms of the first guinea-pig affected were those of a very severe primary toxic reaction with early appearance of marked respiratory embarrassment. The following is the protocol:

PIG 21: *History.*—A 300 gm. animal in a cage with six other pigs, directly beneath infected mice cages.

April 4, 1919: Breathing rather rapidly, with occasional pause and expiratory grunt; inactive; fur roughened; evidently sick.

April 5: At 2 p. m., respirations 200 per minute, labored, almost constant expiratory grunt; occasional cough; pig inactive. Leukocyte count, 11,300; polymorphonuclears, 65 per cent.; mononuclears, 35 per cent.; temperature, 101.8 F. At 6 p. m., respirations 180. At 12 p. m., pig appeared somewhat better, respirations still rapid and labored, however.

April 6: At 3:30 a. m., and at 7 a. m., condition unchanged; still quite rapid respirations with grunting expiration, inactive, fur roughened, but not appearing quite so sick as on previous day. At 1:30 p. m., respirations 170; temperature 100.4 F., evidently improving. At 3 p. m., killed by blow on back of head.

Necropsy.—There was a slight increase of peritoneal fluid; serous surfaces smooth and glistening; no evident pathology in abdomen. The medial, ventral and cephalic lobes of the left lung appeared completely involved in a firm lobular gray consolidation. A similar type of involvement was present in the same lobes on the right side but chiefly central in the cephalic lobe. Both caudal lobes were large, soft and crepitant, appearing normal, except for

moderate emphysema. The cut surface of these lobes, however, disclosed a few small gray areas near the hilus along the main bronchi, and a few punctate hemorrhages in the remainder of the lobe.

Microscopic: Sections revealed a fairly uniform type of pathology with varying degrees of involvement. The gray nodules seen in gross were areas of dense polymorphonuclear alveolar exudate, localized very definitely in the alveoli surrounding terminal bronchioles (Fig. 3). This lesion apparently began at the point of transition of the cuboidal epithelium of the terminal bronchiole to the flat epithelium lining the alveoli of the infundibulum. The infundibulum and surrounding alveoli are seen packed with polymorphonuclears
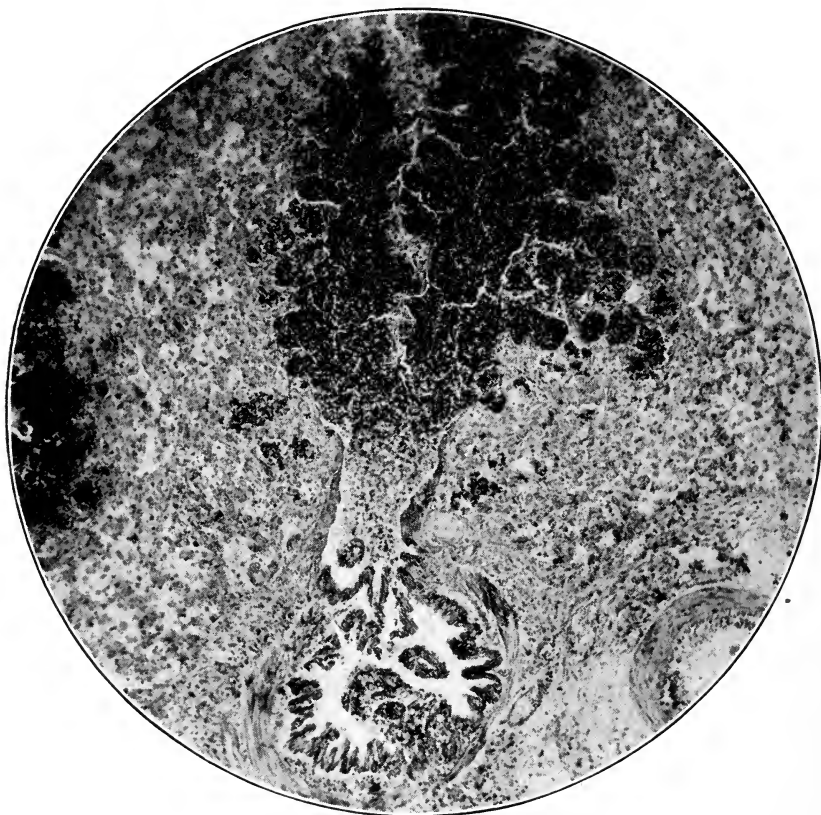

Fig. 3.—Microphotograph of a lung section from guinea-pig 21, showing an advanced infundibular lesion. This consists of an area of dense polymorphonuclear alveolar exudate subtended by a terminal bronchiole. The active process is distinctly delimited by the line of transition from the cuboidal epithelium of the terminal bronchiole to the flat epithelium of the infundibulum. There is no reaction about the bronchus except the general atelectasis and consequent slight cellular infiltration. The bronchial lumen contains only degenerated leukocytes which appear to have drained from the infundibulum.

which have not extended in great numbers into the bronchus but which evidently have blocked the terminal bronchiole. The alveoli beyond this rather sharply localized polymorphonuclear reaction are atelectatic, having a narrowed lumen, enlarged epithelial cells and a content of granular material with a few

large mononuclear cells. The small focal hemorrhages seen in gross section of the caudal lobes are identified as similarly localized areas of infundibular and surrounding alveolar hemorrhage, with blocking of the terminal bronchiole and inclusion of air bubbles in the hemorrhagic exudate. The best examples of this are found surrounding terminal bronchioles near the main bronchus of the lobe, indicating that the progress of the infection is by direct continuity of the bronchial mucosa, the later infection in the caudal lobes probably being controlled to some extent by gravity and distance.

Bacteriologic: A heavy growth of the *Bacillus bronchisepticus* was obtained from the trachea and the left cephalic lobe of the lung. Cultures from the heart's blood, peritoneum, pericardium and right caudal lobe of lung were negative. No other micro-organisms were present.

The following day, April 7, another guinea-pig on the same side of the room was isolated on account of ill defined symptoms of illness. The respirations were not increased, were quite shallow and only slightly irregular. This pig was under constant observation during the afternoon and there was some question from the symptoms whether he was sick or not. Unfortunately, he was killed late that night and no tissues were saved. The gross description of the organs at necropsy, however, gave a diffuse emphysematous hemorrhagic lesion in all lobes of the lungs as the only evident pathology. Cultures were not made.

April 8, a pig was found dead in a cage beneath the mice cages. This cage had been inspected on the previous day and this pig had not been identified as sick, although most careful observations were being made at this time. The protocol follows:

Pɪɢ 22: *History.*—April 8, 1919, found dead, evidently only a short time postmortem. Blood tinged froth was seen in the nostrils.

Necropsy.—Abdomen negative, except moderate vascular injection of viscera. The lungs were voluminous, not collapsing on opening the thorax, and there was an increased amount of clear fluid in both pleural cavities. The left cephalic lobe was mottled with dark red, chiefly central, and pink emphysematous areas, chiefly peripheral. The ventral lobe was a dark red color throughout and more firm. The left caudal lobe was more nearly normal but voluminous and contained scattered small focal areas of apparent hemorrhage. The lobes of the right lung were similar but less involved.

Microscopic: The predominant lesion in all lobes was a marked capillary engorgement with variable serous exudation in the alveoli. The central or hilus portions of the lobes gave evidence of a more severe capillary lesion. In many places there was thrombosis of the capillaries with evident degeneration of the alveolar septums, desquamation of the epithelial cells, beginning infiltration with polymorphonuclear leukocytes and serous exudation into the alveoli (Fig. 4). Alveolar hemorrhage was not prominent. The localization of these areas of most severe involvement did not throw much light on their manner of origin, whether in relation to bronchi or bloodvessels. There was an extreme edema of the perivascular tissue surrounding the larger blood vessels. The bronchi contained an eosin staining coarse granular material. The terminal bronchioles did not show a greater reaction than other regions and did not appear to be blocked by exudate.

Bacteriologic: Lung cultures gave a heavy pure growth of the *Bacillus bronchisepticus*. Sections stained for bacteria with Giemsa's stain demonstrated large numbers of small bacilli in the bronchi and in the more involved regions. In the bronchi they were located along the epithelial border but could

not be found, except rarely, in the bronchial wall. Immediately surrounding the larger bronchi they were especially abundant in the alveoli and the alveolar walls. There appeared to be a similar concentration about the larger veins. The areas of capillary thrombosis always contained many bacilli, not in the thrombosed capillaries but in clumps or within cells in the alveoli or in the alveolar walls in regions of degeneration.

It was at about this time that an attempt was made to check the epidemic by rigid isolation of sick pigs and sterilization of cages,
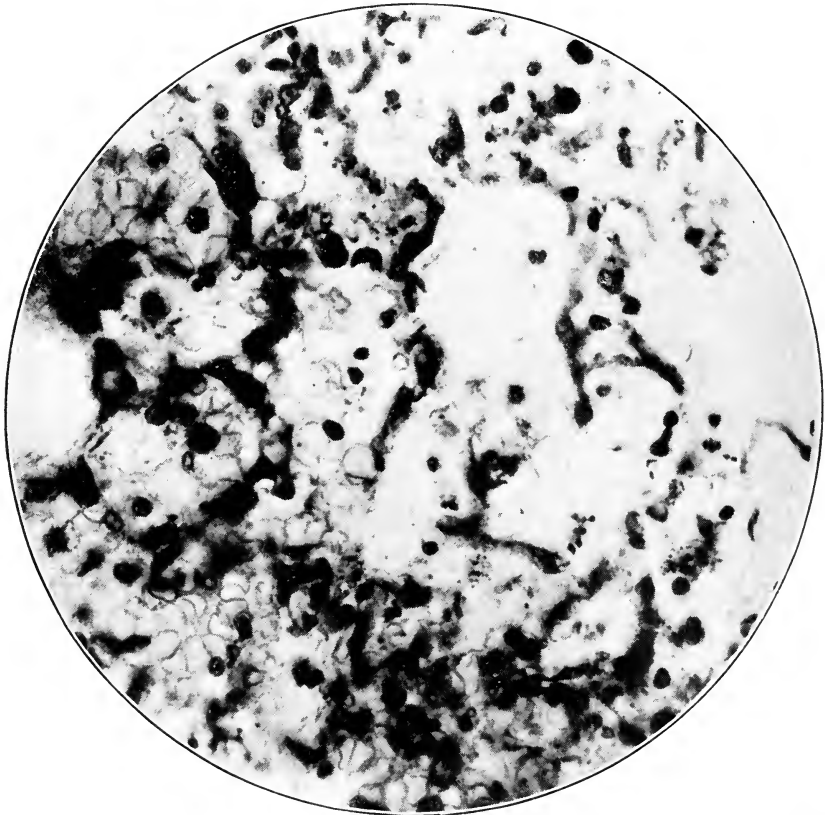

Fig. 4.—Microphotograph of an area of capillary thrombosis in the lung of guinea-pig 22. The thrombi are indicated by the irregular branching darkly stained areas. There is considerable necrosis of the alveolar walls, serous exudation and beginning polymorphonuclear infiltration. Capillary engorgement and hemorrhage are evident at the left side.

with transfer of some of the normal appearing pigs to common outside pens. But pigs continued to become sick, now in the outside pens and on the other side of the animal room. The following protocol is that af a breeding female from the outside pen and illustrates a pneumococcus complication:

PIG 25: *History.*—April 12, 1919, noted inactive and not feeding. That night a miscarriage occurred. The respirations increased moderately during the next two days, the pig becoming gaunt and weak. Killed April 15.

Necropsy.—There was found a massive gray lobular consolidation of both cephalic lobes and a more uniform darker consolidation of the ventral and median lobes. The caudal lobes were emphysematous, did not collapse and presented only small nodules along the main bronchi.

Microscopic: Sections presented a type of pathology somewhat different from that previously found. The predominant lesion was a rather widespread polymorphonuclear alveolar exudate, distinctly lobular in its distribution, yet confluent in many places. Very little fibrin was present, although places were found in which there was the typical fibrinopurulent alveolar exudate of pneumococcus pathology. The most characteristic lesion found in this and other pigs with a secondary pneumococcus infection was focal necrosis of variable size and shape.

Bacteriologic: Lung cultures from the ventral lobes gave a pure growth of the *Bacillus bronchisepticus.* A pneumococcus, tested by inulin fermentation and bile solubility, was recovered from the left median lobe.

The following protocol represents an infection in a newly received group of guinea-pigs, another instance of which is Pig 40. There seemed to be a tendency for acute cases to occur in new stock a few days after their receipt.

PIG 26: *History.*—April 15, noted somewhat inactive, yet of questionable illness. The following morning he was distinctly ill, with roughened fur, rather deep but not increased respirations, and noted occasionally coughing and rubbing his nose. At 5 p. m. April 16, respirations were 100 per minute; temperature, 101.6 F.; leukocyte count, 8,500; polymorphonuclears, 66 per cent.; mononuclears, 34 per cent. He was killed at this time.

Necropsy.—The abdominal organs appeared to be congested, the liver and spleen being a dark red color. On opening the thorax, there was not a very evident lung lesion from the ventral surface. Complete examination, however, showed the greater part of the median and ventral lobes involved by a grayish pink lobular consolidation. Similar lesions were found along the main bronchi in the cephalic and caudal lobes, reaching the surface in very few places.

Microscopic: The lesion in the lungs consisted of a lobular polymorphonuclear alveolar exudate, in places becoming confluent. Small polymorphonuclear lesions at terminal bronchioles, similar to those described for Pig 21, were found in less involved regions. The bronchi contained considerable mucus with a few polymorphonuclear cells. The bronchial epithelium appeared normal. A few small areas of focal necrosis were found in the alveolar lesions, similar to those of Pig 25.

Bacteriologic: Lung cultures from the cephalic lobes gave numerous colonies of *Bacillus bronchisepticus* and a few pneumococcus colonies. Heart's blood cultures were negative.

The following protocol of Pig 27 has seemed to have special significance in the interpretation of the pathology of epidemic pneumonia, as it was an acute toxic case at the height of an animal epidemic, killed at a very early stage and thus demonstrates the primary type of reaction at the onset of toxic symptoms.

PIG 27: *History.*—April 18, 1919. The symptoms of illness first observed at noon were ill defined, a slight inactiveness and indisposition and a watery appearance of the eyes. The respirations were not increased, were quite shallow and apparently normal. The fur was not roughened. It was a very questionable illness. At 3 p. m. the symptoms were more distinct. The pig remained very quiet and the respirations were distinctly abnormal. They were of the short gasping type, not rapid, varying greatly at different times, between 80 and 150 per minute, but more often below 100. There were occasional attacks of severe coughing during which the pig appeared to have great difficulty in breathing, as though suffocating. Between attacks shivering was noted. The temperature was 99.8 F.; leukocyte count, 2,100 per c.cm.; polymorphonuclears, 10 per cent.; mononuclears, 85 per cent.; transitionals, 5 per cent. At this time the pig was killed by a blow on the back of the head. (Note: This method of killing was selected on account of not wishing to enter the factor of a respiratory anesthetic. It, however, does leave the possibility of nasal or pharyngeal hemorrhage which may be aspirated into the larger bronchi. Consequently, such hemorrhage found in the larger bronchi must be disregarded as a possible artefact. A better choice of means of killing might have been made. It is hardly possible that this would confuse in the interpretation of terminal bronchiolar and alveolar lesions since such a death means an immediate cessation of respirations.)

Necropsy.—In both cephalic and ventral lobes there was a grayish, lobular, semitranslucent consolidation along the main bronchi, reaching the surface in only a few places. The remaining peripheral part of these lobes was emphysematous or normal appearing. The medial lobes were completely involved in a fairly uniform gray consolidation. Both caudal lobes presented on the surface and cut section many small punctate hemorrhages, hardly noticeable as abnormal. These lobes were large and did not collapse. Figure 5 is a photograph of a section of the right caudal lobe, passing parallel to the main bronchus, and illustrates very well the above description. The dense hemorrhage in the main bronchus must be disregarded as a possible artefact.

Microscopic: Sections of the gray lobular consolidation along the main bronchi of the cephalic and ventral lobes showed this to be a rather diffuse polymorphonuclear alveolar exudate, yet preserving evidence of its primary localization in the terminal bronchioles, by the denser exudate in these regions and a partial atelectasis of the intervening alveoli. The terminal and smaller bronchioles commonly appeared dilated with a dense polymorphonuclear exudate. The widely spread small punctate hemorrhages of the large caudal lobes were found to be small areas of infundibular hemorrhage. The bronchus and terminal bronchioles leading to each of these areas were normal appearing, except for a distinct indication of a hyperactive secretion of mucus by the bronchial mucosa with numerous globules in the lumen and some darkly staining granules which could not with certainty be identified as bacteria. The hemorrhagic lesions, when seen at selected places cut parallel to a terminal bronchiole (Fig. 6), or followed in serial sections, were constantly found to begin at the site of transition of the columnar or cuboidal epithelium of the terminal bronchiole into the flat epithelium of the infundibular alveoli, and extend in triangular or treelike manner from this stem. This hemorrhage apparently effectually blocked the terminal bronchiole, extending a variable distance into it. The only other type of lesion in these caudal lobes was a replacement of the focal infundibular hemorrhages by polymorphonuclear cells, this occurring more frequenty in the left caudal lobe near the hilus, indicating a slightly older process in this region. Areas with partial replacement by polymorphonuclear cells were found, this taking place first in the immediate region of the terminal bronchiole and later in the periphery of the hemorrhagic lesion.

Bacteriologic: Lung cultures from both cephalic and caudal lobes gave abundant pure growth of the *Bacillus bronchisepticus.* Heart's blood cultures were negative.

Guinea-pig 27 furnished very good material for the study of the mode of infection in this epidemic of pneumonia, since the caudal lobes presented widely distributed focal infundibular hemorrhagic lesions, representing a very early stage, and in one region showed the transition of these hemorrhagic lesions to a polymorphonuclear
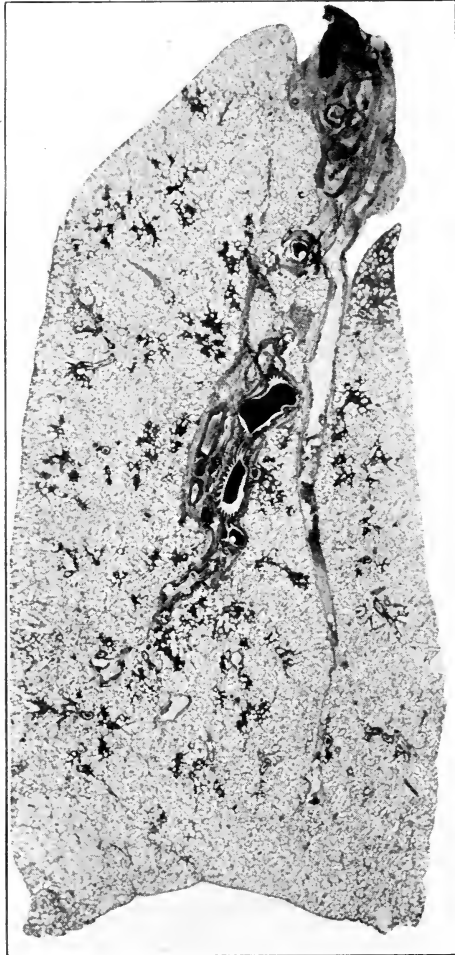
Fig. 5.—Microphotograph of a section of an entire caudal lung lobe of guinea-pig 27, showing the widespread infundibular hemorrhagic reaction during the early acute toxic stage of the pneumonia. Each small dark area represents an infundibular hemorrhage of the type illustrated by Figure 6. There is no other lesion in this lobe.

type. The bronchi in general were normal appearing, except that the lumen most commonly was flooded with red blood cells. In a few bronchi only mucus globules were found, or polymorphonuclear

leukocytes and mucus where the bronchus subtended a polymorpho-
nuclear infundibular lesion.

Some indication of the mode of infection should be given by the
location of the bacilli during the various stages of the primary focal
lesion.   For this study of bacteria in section Wolbach's modification
of Giemsa's stain was found most useful.[4]   The *B. bronchisepticus* in
tissue growth is very small, comparable in size to the influenza
bacillus.   Previous writers have located the bacilli along the ciliated
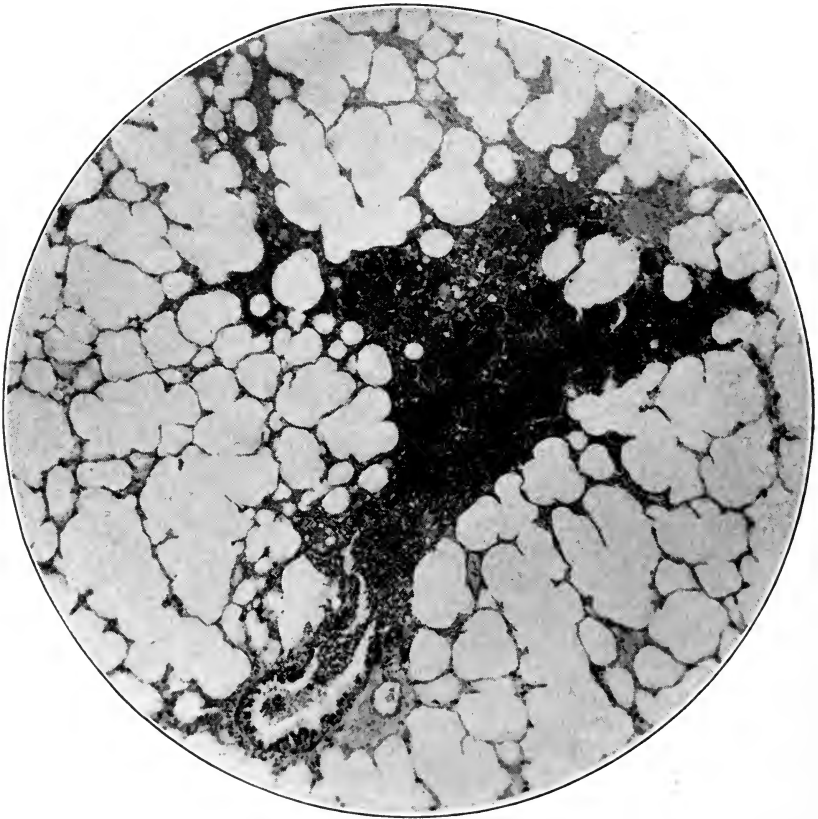
Fig. 6.—Microphotograph of a terminal bronchiole selected from the sec-
tion illustrated by Figure 5, guinea-pig 27.   The dark area consists of red
blood cells, except that there are a few polymorphonuclear leukocytes in the
immediate region of the terminal bronchiole and within the lumen.   ·

border of the bronchial epithelium, but have not recognized the type
of infundibular lesion presented by the entire caudal lobe of Pig 27,
nor attempted correlation of the location of the bacilli with the stage
of the infection.

4. Wolbach, S. B.: Studies on Rocky Mountain spotted fever, J. M. Res.
41:1, 1919.

The pathologic evidence presented by Pig 27 indicates that the infection descended the bronchi without producing a manifest lesion until it reached the thin pavement epithelium of the infundibuli, where focal hemorrhages resulted which flooded the smaller bronchi. Search for bacteria in these bronchi revealed a considerable number of very small deeply staining granules at the epithelial border, partly free but frequently appearing to adhere to globules of mucus which were being actively extruded from the epithelium. The location of the greater number of these granules was at the tips of the folds of the mucosa. They could be traced into the terminal bronchioles

Fig. 7.—Microphotograph of bronchial mucosa from guinea-pig 27, to show the *Bacillus bronchisepticus* located between the folds of the mucosa. This area was selected from a small bronchus which subtended a polymorphonuclear infundibular lesion, similar to that illustrated by Figure 3. The bacilli are seen as small dots at the border of the epithelium.

and were found in the hemorrhagic exudates of the infundibuli. The identity of these granules is difficult to establish. The presence of the bacillus bronchisepticus in both caudal lobes was proven by culture, numerous colonies being obtained from a drop of lung juice withdrawn by capillary pipette through seared lung surface. The granules described were the only evidence of bacteria that could be found in relation to the earliest hemorrhagic infundibular lesion.

The *B. bronchisepticus* was easily and certainly found in bronchi which subtended polymorphonuclear lesions.   These bronchi usually contained mucus globules and cell detritus of degenerated polymorphonuclear leukocytes which most probably had descended from the infundibular lesion, as there was no evidence of a peribronchial reaction or the passing of leukocytes through the bronchial epithelium. The bacilli were found chiefly in the depressions between the folds of the mucosa (Fig. 7).   They were quite numerous in places and situated in contact with the ciliated border of the epithelial cells. Rarely could bacilli be identified in   the central bronchial exudate or in the infundibular lesion.   In the larger bronchi at the hilus the bacilli were more uniformly distributed along the epithelial surface. The location of the bacilli between the folds of the mucosa in the smaller bronchi may represent the persistence of the infection only in the more protected regions near the infundibular lesion.

The following protocols, given in brief, will indicate the course of events in succeeding days of the epidemic:

Pig 28: *History.*—April 18, 1919, an old breeding pig isolated on the preceding day on account of questionable illness. Leukocyte count, 10,700; polymorphonuclears, 66 per cent.; mononuclears, 34 per cent.; temperature, 101.6 F.; respirations 100 per minute. Killed by a blow on the head.

Necropsy.—Abdomen negative. Left cephalic lobe of the lungs completely involved by a gray type of consolidation. No hemorrhagic areas. Remaining lobes apparently normal except for marked anthracosis.

Microscopic: The involved lobe showed irregular areas of polymorphonuclear alveolar exudate, with intervening atelectasis or confluence of lesions. There also were areas of necrosis with abscess formation.

Bacteriologic: Cultures of the involved lobe gave a pneumococcus, pleural fluid and heart blood negative.

Pig 29: A young pig, weight 200 gm., found dead April 20.

Necropsy.—All lobes showed a dark red lobular involvement.

Microscopic: The lesion chiefly was that of capillary engorgement, centrally distributed with, in places, serous exudation or alveolar hemorrhage. One small bronchus was found dilated with polymorphonuclear cells and surrounded by polymorphonuclear alveolar exudate. Cultures from caudal lobes and trachea gave numerous colonies of the *B. bronchisepticus.*

Pig 30: *History.*—This pig was noted coughing April 20. He remained quiet but appeared active and irritable when disturbed. The respirations were not rapid, 100 per minute, but were of the short gasping type, irregular and interrupted by violent paroxysms of coughing as though suffocating. Shivering was noted. The temperature was 103 F.; leukocyte count, 14,000; polymorphonuclears, 23 per cent.; mononuclears, 77 per cent. He was killed by a blow on the head.

Necropsy.—The right cephalic, ventral and median lobes were completely involved in a moderately firm gray lobular consolidation. The right caudal lobe had a similar irregular area of gray consolidation at the hilus and along the main bronchus, but the remainder of the lobe was emphysematous and contained a few widely scattered punctate hemorrhages. All of the lobes of the left lung were emphysematous, did not collapse, and showed on the surface and cut section numerous small hemorrhagic spots, with no evident areas of gray involvement. The mucosa of the trachea and main bronchi was pale

and normal appearing. These did not contain blood but a blood clot was found in one of the first subdivisions of the left bronchus, subtending a small area of alveolar hemorrhage.

Microscopic: The gray lesions in the right lobes consisted of a dense poly-morphonuclear infiltration in the infundibuli and surrounding alveoli, extend-ing down into the dilated bronchioles. The intervening alveoli contained a few polymorphonuclear and mononuclear cells and appeared atelectatic. The per-ipheral part of the right caudal lobe and all lobes of the left lung, which showed rather uniformly distributed small hemorrhagic spots in gross, presented a type of lesion identical with that described in detail for the caudal lobes of Pig 27. These small hemorrhages were located in the infundibuli and the hemorrhagic exudate extended a variable distance down the bronchi. The mucosa of the bronchi was normal appearing except for evidence of active secretion of globules of mucus into the lumen. There was no dilatation of the bronchi or peribronchial reaction of any kind.

Bacteriologic: Cultures from the trachea and larger bronchi gave a heavy and pure growth of the *B. bronchisepticus*. Cultures from the blood cast in the left bronchus gave moderate numbers of the *B. bronchisepticus*. Culture from the right cephalic lobe of the lung gave a few colonies of the *B. bronchi-septicus* and culture from a hemorrhagic area of the left lung was negative. Examination of Giemsa stained sections for the location of the *B. bronchi-septicus* presented the same difficulties as in Pig 27. Numerous very small darkly stained granules were found near the folds of the mucosa, commonly adhering to globules of mucus, in the early hemorrhagic stage of the lesion. These could not positively be identified as bacteria. However, in the bronchi subtending the older polymorphonuclear lesions definite bacilli were found between the folds of the mucosa along the ciliated border of the cells.

Pig 31: Found dead April 21, several hours postmortem.

Necropsy.—The lungs were found diffusely hemorrhagic, with evident laking of blood and marked empyema. There were no areas of gray consolidation.

Microscopic: Marked postmortem degeneration with desquamation of the bronchial epithelium. There appeared to be a diffuse capillary engorgement with central alveolar hemorrhage or serous exudation. Focal lesions could not be identified.

Bacteriologic: Cultures were overgrown by a spore-bearing contaminant.

Pig 32: *History.*—Observed ill April 28; respirations, 125 per minute, irreg-ular and deep Pig quiet but active when disturbed. Leukocyte count, 15,500; polymorphonuclears, 10 per cent., mononuclears, 90 per cent. Killed by blow on head.

Necropsy.—There was a central lobular gray consolidation in all lobes with a few peripheral puncture hemorrages.

Microscopic: Material was lost in process of embedding.

Bacteriologic: *Bacillus bronchisepticus* recovered in pure culture from the right caudal and cephalic lobes.

Pig 33: *History.*—May 5, had been under observation two days on account of inactiveness and abnormal respirations, 114 per minute, irregular and deep; leukocyte count, 17,700; polymophonuclears, 73 per cent., mononuclears, 27 per cent. Killed by blow on head.

Necropsy.—The cephalic and ventral lobes on both sides showed a lobular grayish red consolidation. Both caudal lobes were emphysematous and con-gested but with no distinct pneumonic foci.

Microscopic: The lesion in the cephalic and ventral lobes was a rather diffuse lobular polymorphonuclear alveolar exudate, most dense in the region of terminal bronchioles. Intervening uninvolved alveoli were atelectatic. A purulent pleurisy was found in section, not noted in gross. The larger bronchi contained no pus but a considerable amount of mucus. There was evidence of a

previous healed infection in the lung, presented by dense accumulation of lymphoid cells rather widely distributed and having a relation either to blood vessels or obliteraed bronchi.

Bacteriologic: Lung cultures gave the *B. bronchisepticus,* heart blood culture negative.

Pig 40: *History.*—May 23, 1919, found dead, not noted ill on previous day, although cage was examined for sick pigs. He was one of twelve pigs that had been received a few days previously from outside stock. The entire lot had been kept separate in clean cages.

Necropsy.—The lungs were very red and emphysematous. More extensive involvement in the central part of the lobes. The cut surface exuded blood stained fluid and air bubbles. No gray areas found.

Microscopic: Sections showed chiefly capillary engorgement, with serous or hemorrhagic alveolar exudate in the central region of the lobes.

Bacteriologic: Tracheal culture positive for the *B. bronchisepticus,* lung cultures negative.

Pig 48: This pig was a normal animal, killed May 17, and a lesion was found in the lungs which probably represents the final result in the healing of the focal infundibular lesions. Nothing was noted in gross but microscopic section revealed small foci of lymphoid cells distributed throughout the caudal lobes of the lung. These had no very constant relation to bronchi or blood vessels but occasionally were seen to be located at the termination of a bronchiole. Similar lesions were noted in Pig 33.

Pig 50: This pig was one which had gone through the epidemic without having developed evident illness. He was killed May 28, 1919. The lungs in gross appeared normal, except that the main bronchi appeared quite prominent in section. Microscopically these larger bronchi were found with a moderate peribronchial infiltration of lymphoid cells, a hyperplastic mucosa and an irregular lumen, evidence of a previous chronic bronchial infection with dilatation. Tracheal cultures gave a heavy growth of the bacillus bronchisepticus. Lung and heart blood cultures negative.

BACTERIOLOGY

This epidemic of pneumonia in mice and guinea-pigs was studied chiefly from the standpoint of pathology, hence the bacteriologic data add little toward the establishment of the etiologic micro-organism of the disease. However, the *B. bronchisepticus* was recovered sufficiently often from the trachea and lungs to indicate that we were dealing with the same type of epidemic disease interpreted by other investigators to be caused by this bacillus.

The first identification of this micro-organism in relation to this epidemic was in a mouse with the symptoms and pathology of purulent bronchitis. The infection among the mice had been noted several weeks previously but bacteriologic or pathologic observations were not made. The *B. bronchisepticus* in this and subsequent cases was identified by morphologic and cultural characteristics. The primary growth on blood agar plates was much less during the first twenty-four hours than at the end of forty-eight hours or in a twenty-four-hour subculture. The larger colonies were a grayish white color and emulsified readily in salt solution. Smears from the primary

growth revealed a very small gram-negative bacillus, somewhat comparable to the influenza bacillus in size and morphology. In subcultures the size was considerably larger. These bacilli were actively motile in bouillon culture and gave a diffuse clouding. They grew readily on ordinary media. They did not ferment dextrose, lactose, galactose, saccharose, maltose, mannite, dextrin or inulin in Hiss' serum water media. They were distinctly aerobic and on potato slants gave a rich yellowish brown growth within forty-eight hours. All of these qualities are in agreement with the micro-organism described by Ferry,[2] McGowan,[5] Torry[6] and Smith[7] as the etiologic factor in common epidemics of distemper and pneumonia in laboratory animals and called the *Bacillus bronchisepticus*.

TABLE 1.—Epidemic Pneumonia in Mice. Necropsies.

Date	Number	Bacillus bronchisepticus	Type of Pneumonia
3/27/19	1	+	Purulent bronchitis
4/ 9/19	2	—	Purulent bronchitis
4/ 9/19	3	+	Purulent bronchitis and lobular
4/ 9 19	4	—	Purulent bronchitis
4/11/19	5	+	Purulent bronchitis, lobar and hemorrhagic
4/13/19	6	—	Lobular and hemorrhagic
4/13/19	7	—	Hemorrhagic
4/13/19	8	—	Purulent bronchitis and hemorrhagic
4/18/19	9	—	Hemorrhagic
4/18/19	• 10	—	Lobular and hemorrhagic
4/18/19	11	—	Lobular and hemorrhagic
4/18/19	12	+	Purulent bronchitis and hemorrhagic
4/18/19	13	—	Hemorrhagic
4/18/19	14	—	Hemorrhagic and lobular
4/24 19	15	—	Hemorrhagic and purulent bronchitis
4/24/19	16	—	Purulent bronchitis
4/27/19	17	—	Negative
4/27/19	18	—	Hemorrhagic
4/27/19	19	—	Hemorrhagic and purulent bronchitis
4/27/19	20	+	Hemorrhagic
6/ 1/19	21	—	Lobular, hemorrhagic and purulent bronchitis
6/ 1/19	22	—	Lobular, hemorrhagic and purulent bronchitis
6/ 1/19	23	—	Lobular, hemorrhagic and purulent bronchitis
6/ 1/19	24	+	Purulent bronchitis and hemorrhagic

Lung cultures were made from twenty-four mice submitted to necropsy during the epidemic, with recovery of the *B. bronchisepticus* in only six of these, or 25 per cent. (Table 1). Tracheal cultures were not made from the mice which may partly account for the low percentage of positive cultures, since it is recognized that lung cultures are commonly negative in this disease when taken from the hemorrhagic lesions or healing processes.[6]

5. McGowan, J. P.: A laboratory epidemic of distemper, J. Path. & Bacteriol. **15**:372, 1910.

6. Torrey, J. C., and Rahe, A. H.: Studies in canine distemper, J. M. Res. **17**:291, 1913.

7. Smith, Th.: Some bacteriologic and environmental factors in the pneumonias of lower animals, with special reference to the guinea-pig, J. M. Res., **24**:291, 1914.

The *B. bronchisepticus* was recovered more constantly from the guinea-pigs (Table 2). Fifteen pigs which developed symptoms of the epidemic disease were submitted to necropsy. Lung or tracheal cultures were made in fourteen of these, with recovery of the *B. bronchisepticus* in twelve. Of the two negative cultures, one contained only a pneumococcus and the other was overgrown by a spore bearing bacillus. The pneumococcus was recovered in three cases, each time from lung culture and in one of which there was a pneumococcus peritonitis.

TABLE 2.—EPIDEMIC PNEUMONIA IN GUINEA-PIGS. NECROPSIES.

Date	No.	Bacillus bronchisepticus		Pneumococcus		Type of Pneumonia
		Tr.	L.	Tr.	L	
4/ 6/19	21	+	+	—	—	Polymorphonuclear and hemorrhagic infundibular pneumonitis
4/ 7/19	..	..	..	..	..	Hemorrhagic
4/ 8/19	22	..	+	..	—	Serohemorrhagic
4/15/19	25	..	+	..	+	Lobular with necrosis
4/16/19	26	..	+	..	+	Infundibular, lobular, necrosis
4/18/19	27	..	+	..	—	Infundibular and lobular
4/18/19	28	..	—	..	+	Lobular with necrosis
4/20/19	29	+	—	—	—	Serohemorrhagic
4/20/19	30	+	+	—	—	Infundibular and lobular
4/21/19	31	..	..	..	..	Serohemorrhagic
4/28/19	32	..	+	..	—	Lobular
5/ 5/19	33	+	..	—	..	Lobular and healed infundibular
5/ 5/19	34	+	..	—	..	Lobular
5/13/19	35	+	..	—	..	Serohemorrhagic and lobular
5/23/19	40	+	..	—	..	Serohemorrhagic

Twenty apparently normal pigs were killed during the subsidence of the epidemic. Tracheal or lung cultures in these gave the *B. bronchisepticus* in eleven cases, frequently in abundant pure culture. A Type II pneumococcus was recovered from one pig.

The location of the bacilli in the tissues studied in microscopic section has been presented in detail in connection with the protocols, especially that of Pig 27.

DISCUSSION

The observations in this epidemic of pneumonia present two subjects for discussion. The first is the interpretation of the course and pathology, strictly confined to the animal epidemic. The other is the significance of these observations in the interpretation of human epidemics of pneumonia.

In this animal epidemic the infection apparently began as nasal infection or distemper among mice which were in very crowded quarters. Later it became transformed into a predominantly bronchial infection which in the more severe cases presented the symptoms and pathology of purulent bronchitis. The next step in the course of the epidemic was a change to a fulminating toxic pnemonia with

very few respiratory symptoms and an emphysematous serohemorrhagic lung lesion. The subsidence was marked by a return of the predominant respiratory symptoms, but greatly varied lesions were found in the lungs, even of single animals, representing all stages from irregular areas of hemorrhage or polymorphonuclear exudate to purulent bronchitis or lobes with old obliterative bronchial lesions. The mortality rate was not very high among the mice and a large percentage probably became infected without being identified as ill. This was supported by almost invariably finding old lesions in the smaller lobes of supposedly normal mice killed late in the epidemic, and frequently finding active or even hemorrhagic lesions in mice that appeared quite well. A recurrent outbreak of the fulminating hemorrhagic pneumonia appeared in a few mice cages during the decline of the main epidemic, illustrating the possibility of a more virulent infection being superimposed on an existing or previous infection, as old lesions were found in conjunction with the hemorrhagic lesions in most of these mice.

The infection appeared among the guinea-pigs only after it had been prevalent among the mice several weeks. An environmental factor in the transmission of the infection is indicated by the fact that the first pigs affected were directly beneath the mice cages and the infection remained localized on this side of the animal room until an attempted cleaning spread normal appearing but evidently infected stock to other cages and pens. In the transmission of the infection from the mice to the guinea-pigs the stage of pneumonia appearing in the first pigs affected corresponded to that of the mice at that time. The distemper and the long period of chronic illness with marked respiratory embarrassment characteristic of purulent bronchitis did not occur in the pigs. The onset in the first pig affected was sudden and toxic.

The predominant lesion in this and several other pigs of the early nonfatal cases was a focal infundibular hemorrhage or polymorphonuclear exudate. This began at the point of transition from the cuboidal epithelium of the terminal bronchiole to the flat respiratory epithelium of the infundibulum. It extended a variable distance into the surrounding alveoli and appeared to discharge into the terminal bronchiole, effectually blocking this in many instances.

The most interesting and most completely studied example of this type of pneumonia was Pig 27, killed at a very early stage when marked depression was evident. Both caudal lobes contained widely spread small infundibular hemorrhages. These focal hemorrhages would seem to represent the characteristic initial lesion of the early or milder cases at the beginning of the predominantly toxic stage of this epidemic of pneumonia. The location of this lesion, its evident

older stage in the smaller more dependent lobes or along the main bronchi, and the generally normal appearing bronchi, would indicate a descending bronchial surface infection resulting in a toxic inflammatory reaction only when it reaches the thin respiratory epithelium of the infundibuli and thus comes in intimate contact with the blood capillaries. The first reaction, when there is sufficiently extensive involvement to produce systemic effects, is that of a severe toxemia, chill, prostration, slow irregular respiration and leukopenia. The second reaction is a respiratory embarrassment, due to the blocking of a sufficient number of terminal bronchioles to give symptoms of suffocation. The replacement of the primary hemorrhagic exudate with polymorphonuclear leukocytes is accompanied by a moderate blood leukocytosis. It is significant that all of the pigs presenting the focal infundibular pathology were killed. Those which died after several days illness presented confluent or lobular areas of polymorphonuclear exudate and those which died during the night without having been identified as ill in the previous day presented a more diffuse capillary engorgement, serous exudation and hemorrhage.

The pathology of these rapidly fatal cases was radically different from the infundibular pneumonitis occurring at the same time. This consisted of a more diffuse capillary lesion, most marked in the central or hilus portions of the lobes. It varied from a simple engorgement with slight serous exudation to capillary thrombosis, necrosis of the alveolar walls and hemorrhage into the alveoli. The relation of the bacteria to the more severe lesions indicated a diffuse hilus invasion probably by lymphatic channels but not clearly indicated. Older stages of this same type of lesion in more protracted cases seemed to be represented by irregular confluent areas of polymorphonuclear exudate and necrotic areas with bordering polymorphonuclear infiltration, representative of the places of capillary thrombosis. The difference between this type of pathology and the focal infundibular type could be explained by the increase of virulence of the invading micro-organism until it is enabled to invade diffusely through the bronchial mucosa and spread by lymphatic channels.

The subsidence of the epidemic among the guinea-pigs gave a great variety of lung lesions, as was observed among the mice Hemorrhagic lesions were superimposed on old obliterative lesions. In many apparently normal pigs killed after the epidemic had subsided old lung lesions were found, the commonest being numerous focal accumulations of lymphocytes throughout a lobe of the lung. These probably represented replacement of the focal infundibular polymorphonuclear lesions by mononuclear cells. A few cases were found with the characteristic lesion of healed purulent bronchitis.

The predominant micro-organism recovered in lung and tracheal cultures was the *Bacillus bronchisepticus,* most commonly in pure culture but in a few cases complicated by a pneumococcus. The bacilli could not positively be identified in sections of lung during the earliest stage of infundibular hemorrhagic reaction, but numerous small granules located on the folds of the bronchial mucosa and adhering to mucus globules suggest strongly their identity as bacteria.

These observations on the course and pathology of an animal epidemic of pneumonia seem to be of significance in the interpretation of human epidemics of pneumonia. The recent epidemic of streptococcus pneumonia in the Army corps is the one most completely studied and best understood in this country. This epidemic most probably took its origin from the prevalent streptococcus pharyngitis and bronchitis which preceded the more severe pneumonia.[8] The first stage of the epidemic of pneumonia was recognized and reported.[6] It was characterized by a fairly uniform type of pathology, that of purulent bronchitis, and had a common association with measles. As the virulence of the streptococcus increased a more diffuse lobular pneumonia occurred more frequently and finally true epidemics of streptococus pneumonia occurred without any relation to measles.[9] These epidemics developed rapidly, ran a course of six to eight weeks and the cases presented a predominantly toxic reaction with fulminating course and frequently a diffuse hemorrhagic lung lesion. During the subsidence of the epidemics a greater variety of pathology was encountered, with more cases of lobular pneumonia or interstitial bronchopneumonia as defined by MacCallum. Thus, if the entire course of the streptococcus infection is followed, it is found to have developed along a course very similar to the animal epidemic of pneumonia: from a prevalent mild pharyngeal and increasingly bronchial infection through a period of purulent bronchitis, to an independent epidemic of lobular and hemorrhagic pneumonia, with subsidence through somewhat similar stages in reverse order. This similarity with the course of events in the animal epidemic is significant of the life history of an epidemic of pneumonia.

8. Cole, R.: Etiology and clinical features of the pneumonia occurring at a base hospital, J. A. M. A. **70**:1146 (April 20) 1918. Irons, E. E., and Marine, D.: Streptococcal infection following measles and other diseases, J. A. M. A. **70**:687 (March 9) 1918.

9. MacCallum, W. G.: Pathology of the epidemic streptococcal bronchopneumonia in the Army camps, J. A. M. A. **71**:704 (Aug. 31) 1918. Miller, J. L., and Lusk, F. B.: Epidemic of streptococcus pneumonia and empyema at Camp Dodge, Iowa, J. A. M. A. **71**:702 (Aug. 31) 1918. Lucke, B.: Postmortem findings in measles bronchopneumonia and other acute infections, J. A. M. A. **70**:2006 (June 29) 1918.

With this possible analogy in view it is most interesting to consider the pandemic of influenza and influenzal pneumonia in this light. The origin of the pandemic from all accounts seems to have been in Europe and most probably in the military camps, as the same environmental factors were present there as in the camps of this country where the epidemic of streptococcus pneumonia developed. A fact which immediately comes to the attention is that "there was prevalent during the late winter and early spring of 1916-1917, in the camps of northern France a severe type of bronchial infection, with a symptom complpex quite distinctive, very fatal, and which assumed such proportions by the end of January, 1917, as to constitute almost a small epidemic."[10] This disease presented the typical picture of purulent bronchitis and the predominant micro-organism recovered from the lungs and bronchial exudate was the influenza bacillus, with the pneumococcus playing an important secondary rôle and only a comparatively rare hemolytic streptococcus. The investigators[10] concluded that this disease was caused by the influenza bacillus and noted the fact that a mild influenza epidemic was actually in progress at that time.

This purulent bronchitis disappeared during the summer of 1917 but recurred during the winter of 1917-1918.[11] The chief problem during that winter, however, was a disease or diseases commonly called "P. U. O," (pyrexia of unknown origin), claimed by many to be a capillary bronchitis and suggestive of an atypical influenza.[12] Following this prevalence of "P. U. O." came in April and May, 1918, the first recognition of a widespread epidemic of influenza in the first and second English Armies in France.[13] In July the pandemic quality and increasing severity of the infection were evident,[14] it reaching this country the latter part of August with the well known severe toxic symptoms of onset and hemorrhagic pulmonary complications.[15] The preceding course of events suggests very strongly the gradual development of influenza in the camps of Europe through

10. Hammond, J. A. B., Rolland, W., and Shore, T. H. G.: Purulent bronchitis, Lancet **2**:41, 1917. Abrahams, A., Hallows, N. F., Eyre, J. W. H., and French, H.: Purulent bronchitis. Its influenzal and pneumococcal bacteriology, Lancet **2**:377, 1917.

11. McWalter, J. C.; The phenomena of purulent bronchitis, Brit. M. J. **1**:119, 1918. Eyre, J. W. H., and Lowe, C. E.: Prophylactic vaccination against catarrhal affections of the respiratory tract, Lancet **2**:485, 1918.

12. Pasteur, W., and Hudson, B.: A clinical contribution to the study of P. U. O., Lancet **1**:95, 1918. Annotation: Camp infections, Lancet **1**:810, 1918.

13. Influenzal Committee: The influenza epidemic in the British armies in France, 1918, Brit. M. J. **2**:505, 1918.

14. Maude, A.: Influenza and purulent bronchitis, Lancet **2**:324, 1918.

15. Keegan, J. J.: The prevailing pandemic of influenza, J. A. M. A. **71**: 1051 (Sept. 28) 1918.

a well defined stage of purulent bronchitis, a transition to the stage of infundibular pneumonitis (P. U. O.) and its final development into the stage of acute toxic hemorrhagic pneumonia.

This analogy might be extended further to include pneumococcus pneumonia, in which the well known pneumococcus bronchopneumonia of children would be representative of the developmental stage leading to the later acute toxic lobar pneumonia of young adults.

It is recognized that many features of epidemic pneumonia remain yet to be explained and established before acceptance should be given to the analogy presented in this paper. However, the recognition that epidemics have several stages in their development, each with certain distinctive features of symptomatology and pathology, should lead to a broader conception of epidemic diseases.

SUMMARY

1. This animal epidemic of pneumonia developed through the following stages, fairly well defined by symptoms and pathology:

    (a) Nasopharyngeal infection (distemper).

    (b))Mild bronchitis.

    (c) Purulent bronchitis.

    (d) Infundibular pneumonitis.

    (e) Lobular pneumonia.

    (f) Diffuse serohemorrhagic pneumonia.

    (g) Subsidence in less distinct reverse order.

2. The epidemic of streptococcus pneumonia in the Army camps presented a somewhat similar course of events in its development.

3. The development of the pandemic of influenza can be traced in similar manner.

4. It is suggested that pneumococcus pneumonia should be considered in a similar course of development.

5. The recognition of purulent bronchitis as the natural precursor of an epidemic of acute toxic pneumonia places great significance on the prevalent influenza bacillus purulent bronchitis in the army camps of Europe during the winter of 1916-1917 and supports the view that the influenza bacillus is the cause of influenza.

REPORT OF A CASE OF HEMORRHAGIC SMALLPOX

A CONSIDERATION OF THE RÔLE PLAYED BY THE HEMOLYTIC STREPTOCOCCUS *

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The presence of the hemolytic streptococcus in the blood preceding and during the eruptive stage of a case of hemorrhagic smallpox led us to inquire whether this was a common finding in this form of smallpox. A search through the literature failed to give any information on this point. The close association of the streptococcus with variola is well known. In forty necropsies, practically all of which were in severe cases of smallpox, Perkins and Pay [1] found streptococci in the heart's blood and viscera of thirty-eight, or in 95 per cent. of the cases. Of these forty cases three were of the purpuric type, nine of the so-called secondary hemorrhagic type (variola hemorrhagica pustulosa), twenty-four of the confluent type, one discrete, two varioloid and one desiccating. The streptococcus was present in all of the cases except one purpuric and one varioloid case. These same workers examined the blood of twenty patients, before or just after death, and found streptococci present in eleven, or 55 per cent. If we consider only the sixteen more serious cases in this group, streptococci were present in 69 per cent.

Ewing [2] examined the blood after death in twenty-nine cases of smallpox and demonstrated the streptococcus in all. The abundance of the growth was found to be uniformly proportional to the severity of the disease, and in the primary hemorrhagic cases the cultures were remarkably profuse. In five cases cultures of the circulating blood were examined with a negative result. Only one of these cases was fatal. Ewing was greatly impressed by the early appearance and enormous development of the streptococcus infection in variola, especially in the primary hemorrhagic cases. It seemed to him that the smallpox virus "annihilates resistance" to the growth of the streptococcus.

Arnaud [3] found streptococci in the blood during life in two cases of hemorrhagic smallpox.

1. J. M. Res., **10**:180, 1903.
2. Proc. New York Path. Soc., **1**:72, 1901-2.
3. Rev. de méd., p. 303, 1900.

Councilman[4] reported an intense streptococcus septicemia in all cases of hemorrhagic smallpox examined by him. No mention is made as to whether the organism was hemolytic or not. He regarded[5] the bacterial infection as more important in bringing about a fatal termination than the specific parasite.

Klein[6] refers to a statement by another English worker, Dr. Maurice, who asserted that in a large number of cases of hemorrhagic variola he found in the blood "septic organisms." From this he concluded that it is the entrance of such "septic microbes" into the blood which converts an ordinary case of smallpox into one of hemorrhagic smallpox. Klein believes this explanation is incorrect and argues that he has cultured the blood in a number of fatal cases of confluent smallpox and found a considerable variety of micro-organisms. He states that the organisms found in the blood of hemorrhagic smallpox do not differ from those found in the blood of confluent smallpox. Drs. Drysdale and Scholberg are quoted as having found in the majority of cases of fatal variola, *not hemorrhagic,* staphylococci and streptococci in cultures taken from the heart's blood. Klein concluded his report by citing eight cases of hemorrhagic smallpox in which blood cultures were taken. In only one of the cases was the culture taken during life; in this instance the blood was taken from the finger. No organisms were found. Cultures from the other seven cases were taken from the heart's blood post mortem, the elapse of time after death being as long as three days. Of these eight cases (including Nurse T and the Drysdale-Scholberg case) the cultures were negative in four and positive in four. He reported a variety of organisms, *Diplococcus pneumoniae, Streptococcus enteritidis, Streptococcus brevis,* and an organism which he termed *B. myxoides* because of the slimelike growth it produced on agar. The reliability of blood cultures taken several hours post mortem would seem open to question. In short, Klein drew the conclusion that the entrance of organisms into the blood stream was not the determining factor in hemorrhagic variola cases since half of his cases showed no organisms at all and the other half no constant organism. He considered the organism as a secondary invader, an expression of the patient's low resistance to infection.

The classification of hemorrhagic smallpox into the two types, purpura variolosa and variola hemorrhagica pustulosa, is dependent on the time of appearance of the hemorrhage in relation to the exanthem.

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4. Modern Medicine. Osler-McCrae, 1913. Philadelphia, Lea and Febiger. **1**:805.

5. J. M. Res., **11**:358, 1904.

6. Thirtieth Annual Report of the Local Government Board, 1900-1901, London, p. 548.

In purpura variolosa the hemorrhage is primary, occurring before the exanthem, while in variola hemorrhagica pustulosa the hemorrhage is secondary and is not seen until after the variolous lesions have appeared, hemorrhage having taken place into the pustules.   The case described here is one of purpura variolosa.

REPORT OF CASE

History.—The patient was a nurse, 21 years old. The family history was entirely negative. She had measles, chickenpox and whooping cough in early childhood, scarlet fever two years ago. Her first vaccination was done three months before the onset of the variola. This resulted in a very slight local reaction lasting only one or two days. Aside from frequent colds and "bilious attacks," she had always been well. For three days previous to the definite onset of the disease, the patient had noticed more or less headache and general malaise.

March 1, 1920.—First Day: Patient was suddenly taken ill with severe abdominal cramps, headache, backache and vomiting. The temperature was 102 F. There was a profuse discharge of blood from the vagina at this time, but this was not considered seriously, because the menstrual period was due. Within thirty-six hours, the uterine hemorrhage had greatly increased and there was bleeding from the rectum, mouth and nose. After pricking the finger for a leukocyte count it was noted that bleeding continued for several minutes. Blood appeared in the urine, the tongue became swollen and purple, and bright red blood was raised, apparently from the lungs. Blood culture taken at this time, which was before the appearance of any lesions suggesting variola, was reported as showing hemolytic streptococci.

March 3—Third Day: An erythematous rash was seen which extended over the face, arms, chest, and to a less extent over the lower extremities. This was later interpreted as a prodromal rash.

March 4.—Fourth Day: Hemorrhagic areas appeared on the chest, neck, back, and in both axillae, the largest extravasation being one on the right breast. This covered an area about the size of a dollar. At this time there was hemorrhage from all mucous surfaces, and she was raising rusty sputum. Following the application of external heat as treatment for a severe chill, a macular rash was observed on the forehead and arms. For the first time a diagnosis of variola was considered and the patient was transferred to the Contagious Hospital.[7]

March 5.—Fifth Day: Entrance Examination. Patient appears critically ill. She is exhausted and very uncomfortable. There is a very offensive odor. The face, arms and dorsal surfaces of the hands are covered with a confluent maculo-papular rash, and it extends with less intensity over the chest and back. Numerous deep seated palmer and plantar lesions are seen. The papules are hard and shotty and all are in the same stage of development, except a few lesions on the face, which show beginning umbilication. Lesions are present in the mouth, those on the palate and pharynx standing out very prominently. On the right breast is a large purplish area, an extravasation of blood into the deeper tissues. This is well shown in Figure 1, which was made on the seventh day of the disease. Scattered over both arms are occasional small discolored areas varying in size from the diameter of a pea to that of a dime. There are also many petechial hemorrhages on both arms. Clots of blood cover the mucous membranes of the lips, mouth, nose and vagina. The face is greatly swollen and of a purplish hue. The eyes are almost shut, due to the confluent rash

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7. We are indebted to Dr. J. A. W. Johnson of the Homeopathic Hospital for records and laboratory findings up to this time.

over the lids. Aside from an extremely rapid and weak pulse, the heart and lungs are negative. Abdomen negative, liver and spleen not enlarged. Although very ill, the patient's intellect is entirely clear. The urine is bright red with blood.

A provisional diagnosis of hemorrhagic smallpox with septicemia was made.[8] Blood culture showed hemolytic streptococci. With the hope of checking hemorrhage, 10 c.c. of horse serum was injected intramuscularly.

Fig. 1.—Seventh day of the disease. Showing beginning pustulation and hemorrhages into some of the lesions on the face and arms, as well as into the skin between the lesions. See notes of March 6 and 7.

March 6.—Sixth Day: Face still more swollen, eyes shut. The lesions stand out much more prominently, and many on the face, chest, and arms are black, due to hemorrhage into the lesion. Most of the lesions are in the vesicular stage. There is a striking increase in the number of petechial hemorrhages over the arms. Close examination shows these minute hemorrhages to be located

8. Diagnosis of hemorrhagic smallpox confirmed by Dr. Cowie and Dr. Wile.

between and entirely distinct from the pocks. Nausea is still a very prominent symptom. Somewhat less blood in the urine. Blood culture shows hemolytic streptococci.

March 7.—Seventh Day: Hemorrhage not so noticeable, only slight bleeding from the lips. The urine shows less blood. Lesions now all pustular. The hemorrhagic lesions on the face are very prominent. This seems to be the height of the eruption. Picture taken today.

March 8.—Eighth Day: No further hemorrhage noticed today. Lesions in pustular stage. Patient is in better spirits this morning. She takes food very well, and there has been no vomiting. Swelling of the face has definitely receded. No further hemorrhages or petechiae. Lesions in the pustular stage over the entire body. The eyes are still somewhat swollen. Urine is much clearer. Patient complains of severe pain in the right arm. Examination shows a tense swelling of the dorsal surface of the hand, extending half way to the elbow. It is not red, is not hot to the touch, and does not fluctuate.

TABLE 1.—Laboratory Findings

	Day—March, 1920											
	2	3	5	6	7	8	9	10	11	12	13	14
Urine												
Color..............	......	......	red	red	red	straw	red	amb.	amb.	straw	straw	straw
Reaction............	......	......	acid	acid	neu.	neu.	neu.	neu.	neu.	neu.	neu.	neu.
Specific gravity......	......	......	1.020	1.020	1.019	1.019	1.019	1.019	1.019	1.019	1.019	1.020
Albumin.............	......	......	2+	+	+	+	+	+	+	+	+	+*
Sugar...............	......	......	0	0	0	0	0	0	0	0	0	0
Erythrocytes........	......	......	......	......	......	......	......	—	—	—	—	—
Erythrocytes........	......	......	4+	4+	2+	+	+	+	+	+	+	+
Casts...............	......	......	0	0	0	0	0	0	0	0	0	0
Blood												
Erythrocytes........	......	......	4,600,000									
Leukocytes..........	18,000	20,700	26,800	20,000	16,000	15,000	......	12,000	12,000	......	7,000	
Hemoglobin.........			75%	......	75%	......	......	60%				
Small lymphocytes..	13%	26%	8%	6%								
Large lymphocytes..			14%	19%								
Polymorphonuclear neutrophils........	87%	74%	68%	64%								
Polymorphonuclear eosinophils........	......	......	0.5%	1%								
Myelocytes..........	......	......	10%	10%								
Clotting time, Min..	......	......	12							10		
Blood sugar.........	......	......	....	......	......	0.080†						
Blood urea..........	......	......	....	......	......	......	......	0.035g	‡	......		
Blood cultures.......	Hem. strep.	......	Hem. strep.	......	......	......	......	......	......	......	Hem. strep.	

* Lewis-Benedict Method.
‡ Van Slyke modification of Marshall method.

March 10.—Tenth Day: No new hemorrhages. The lesions are far advanced into the pustular stage. The urine approaches a normal color. Severe pain in the right arm.

March 11. Eleventh Day: Lesions show early crusting. No further hemorrhage. Swelling of the face has almost disappeared, the nares for the first time are patent. Right arm still very painful.

March 12.—Twelfth Day: Patient seems very bright this morning. The face has cleared up remarkably, but the lesions over the chest and arms are slow in crusting. Later in the day patient complained of a tightness in her chest. This evening examination shows diminished breath sounds, prolonged high pitched expiration, and moist râles in the right base posteriorly. A few moist râles also heard in the lower left base.

March 13.—Thirteenth Day: No marked change in the eruption, delayed crusting of the lesions over the hands and body. No further hemorrhage. There is a striking change in the patient for the worse. Respirations are increasing.
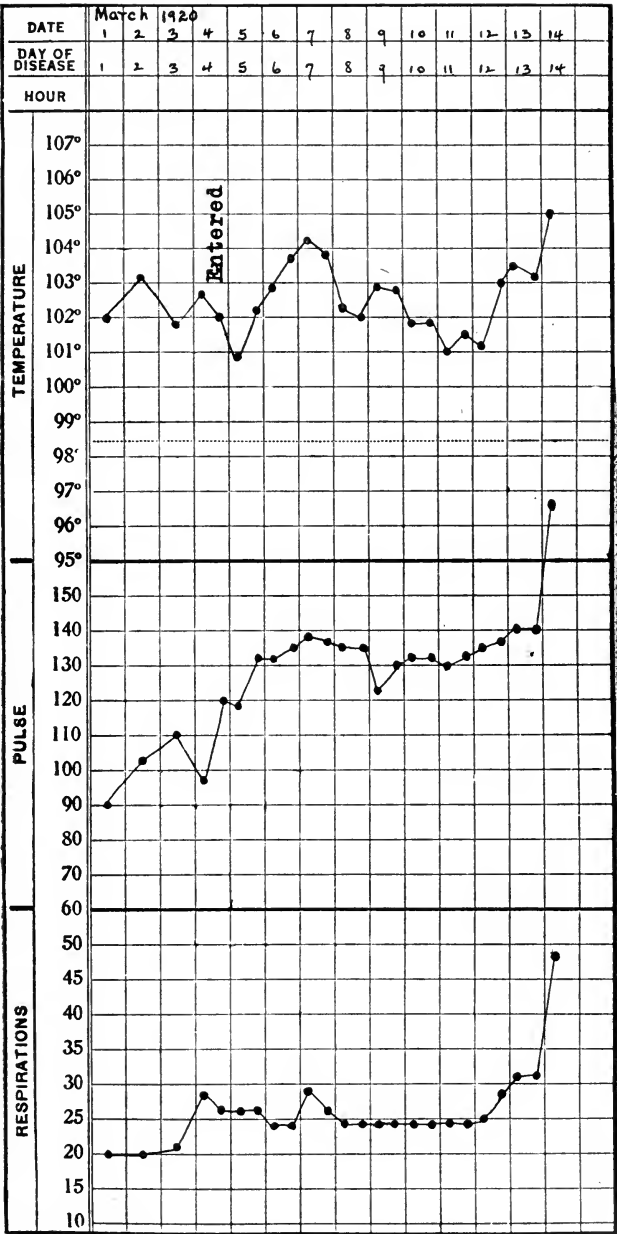
Fig. 2.—Clinical record of temperature, pulse and respiration from first to fourteenth day of disease.

The chest signs are now very distinct and extensive. Leukocytes have dropped from 12,000 to 7,000. The patient fully realizes that she is not so well. She remarks a great deal about her chest, how fast the respirations are, and of the tight feeling. Blood culture shows hemolytic streptococci.

March 14.—Fourteenth Day: No change in the lesions. There is no evidence of hemorrhage anywhere. The urine retains a good color. Condition this morning is extreme, respirations are labored, face and fingers cyanotic. Up to three or four hours before death, the patient's intellect was perfectly clear. She complained of severe pains in the head for which morphin was given. Permission to perform necropsy could not be obtained.

Blood Cultures.—Three c.c of blood was drawn from the median vein and placed in tubes containing 30 c.c. of plain beef broth. Hemolysis of the patient's blood was observed in these tubes in from twenty-four to forty hours. Microscopic examination showed a pure culture of streptococci, arranged in short chains. Rabbit blood agar plates showed isolated colonies with a well defined completely hemoly_ed zone measuring from 2 to 3 mm. in diameter.

COMMENT

We have here presented a typical case of purpura variolosa in which the hemolytic streptococcus was present in the circulating blood as early as the first day of the disease. It is quite probable that it was present in the blood even before the onset symptoms. It apparently developed synchronously with the variola virus and continued throughout the course of the disease, a positive culture having been obtained on the thirteenth day.

In many diseases in which the hemolytic streptococcus is present, there is a tendency to the development of hemorrhage into the viscera, mucous membranes and skin. It will be of great interest to know if the streptococcus so frequently found in variola is of the hemolytic type or only of this type in the cases of hemorrhagic smallpox.

A noteworthy point in this case is the characteristic early appearance of the hemorrhages, the eruption developing and following the normal order through to the crusting stage on the eleventh to the fourteenth day. The case may be regarded as a combination of purpura variolosa and purpura hemorrhagica pustulosa, for as the lesions developed hemorrhage directly into many of them took place. It seems to be well illustrated that this patient conquered her smallpox in spite of the severe secondary infection, but succumbed to the latter when pneumonia, probably of the hemolytic streptococcic type, developed on the twelfth day of the disease.

This lends support to the opinion of Ewing, Councilman and Maurice that the streptococcus infection is of more importance in the fatal termination of variola than the variola virus itself.

RHEUMATIC MYOCARDITIS

A HISTOGENIC STUDY OF THE TYPE CELLS OF THE ASCHOFF BODY *

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In view of the importance of this subject, comparatively little has been reported regarding the histogenesis of the typical cells of the rheumatic myocardial lesions first described by Aschoff.[1] On the other hand, many investigators have directed their attention to the etiology and specificity of the Aschoff body.

Most investigators[2] have agreed that the responsible organism is the *Streptococcus viridans* of Schotmüller, and that the lesions are specific for rheumatic fever. Thalheimer and Rothschild,[3] however, report finding typical Aschoff bodies in cases of chorea without rheumatic history. So far as we are aware their findings have not been confirmed, although the etiologic factor is said to be the same for both diseases.

Workers on the subject have either accepted Aschoff's original theory that the cells are "adventitial wandering cells," or they believe that these cells arise from the intramuscular connective tissue cells of the locality of the lesions. Aschoff (cited by MacCallum[4]) states that nowhere do the type cells arise from muscle cells, but the contrary is suggested by certain statements in the literature. For example, Coombs[5] says that when the cells are multinuclear the nuclei are arranged in the long axis of the cell and the cytoplasm is colored the same shade as muscle cells with Van Giesen's stain. Moreover, Geipel[6] notes that the nuclei of the muscle fibers, broken or eroded by the Aschoff body, or its etiologic agent, are subject to proliferation, the excess of nuclei collecting at the injured end. Structures observed in routine sections of heart muscle from the necropsy discussed in this paper raised the question whether it might not be possible to trace the origin of the characteristic cells in the Aschoff bodies with greater accuracy than has been done hitherto. Evidence which we regard

1. Aschoff: Verhandl. d. deutsch. path. Gesellsch. **8**:46, 1904; Brit. M. J. **2**:1103, 1906.

2. Libman and Coller: Am. J. M. Sc. **111**:516, 1910. Wachter: München. med. Wchnschr. **55**:1101, 1908. Sternberg: Wien. klin. Wchnschr. **32**:522, 1919.

3. Thalheimer and Rothschild: J. Exper. Med. **19**:417, 1914.

4. MacCallum: Textbook of Pathology, 1916, p. 449.

5. Coombs: Brit. M. J. **2**:1513, 1907; Lancet **1**:1377, 1909.

6. Geipel: München. med. Wchnschr. **56**:2469, 1909.

as conclusive is presented herewith, to show that some of the cells, at least, represent degenerated muscle elements. Whether all the cells have the same origin remains an open question. Granted that the cells in question have more than one histogenetic origin, the divergent views of Aschoff, Coombs, Geipel, and others, are explained and correlated.

A brief description of a typical Aschoff body would not be amiss. The nodules are made up of large elements arranged more or less radially about a center, the cells being similar to but larger than the "epithelioid cells" of a tubercle, more nearly resembling the Sternberg
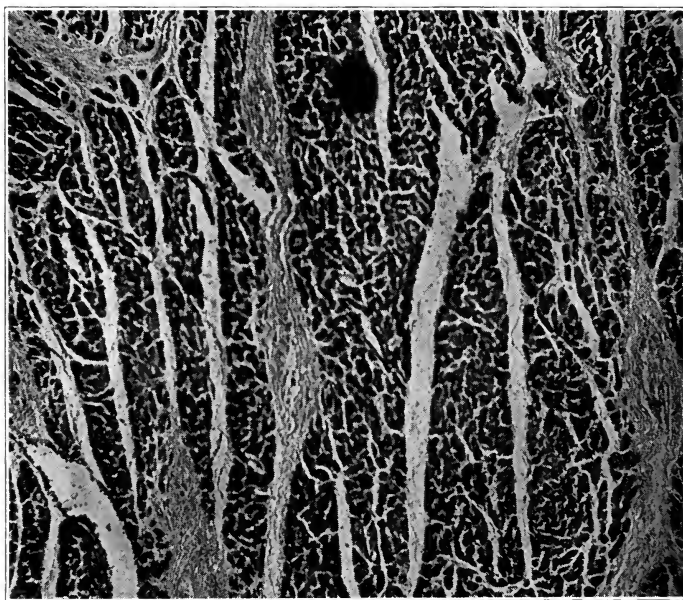
Fig. 1.—Low power field from left ventricle showing eight Aschoff nodules.

giant cells of Hodgkin's disease. The cells are often multinuclear, with rarely more than six or seven nuclei, and are round, fusiform, or an elongated oval shape. The Aschoff bodies are usually close to small vessels or capillaries and are surrounded by a more or less extensive zone containing chiefly neutrophilic with a few eosinophilic leukocytes, some plasma cells and small lymphocytes. All observers agree that the Aschoff elements are atypical cells, most theories placing them as developments from connective tissue cells under the influence of the toxins of the disease. As Huzella [7] says, "The elements of the myocardial rheumatic nodule are cells formed from the myocardial

7. Huzella: Virchows Arch. f. path. Anat. **213**:389, 1913.

connective tissue under the influence of the rheumatic virus, assuming very varying, irregular forms and then degenerating." It is our purpose to show that some, at least, of these cells are derived from muscle elements through degeneration or abortive attempts at regeneration.

The case that was used in the preparation of this paper affords favorable material for studying the histogenesis of these bodies because lesions of all stages were present in the heart.
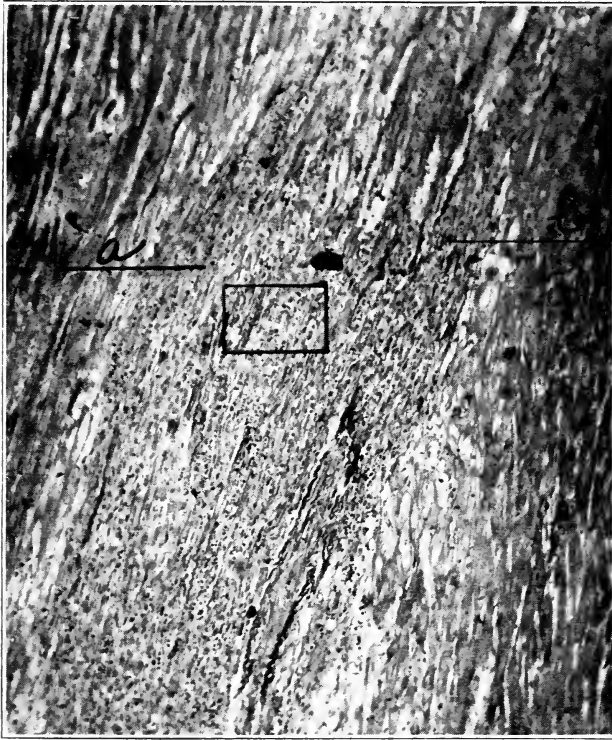

Fig. 2.—From papillary muscle, probably several confluent lesions. Area marked indicates field illustrated in Figure 8. Points indicated by letters referred to in text.

We are indebted to Dr. H. C. Dodge of Boulder for the privilege of studying the case.

REPORT OF CASE

J. F. S., aged 25, a former coal miner, was inducted into the army in June, 1918, and discharged in June, 1919. He claimed that he had never had rheumatism before he was taken into the army. While at Camp Cody he was troubled several times with rheumatism of the feet. After reaching France he suffered several attacks of tonsillitis and rheumatism, the latter, judging from the patient's account, apparently of an inflammatory character, and not confined

to his feet. He was discharged in "good physical condition." About Jan. 1, 1920, he had a severe attack of tonsillitis, and about January 20 a diagnosis of acute dilatation of the heart was made. This last was followed by an attack of acute articular rheumatism. These attacks recurring, he was placed in the University Hospital at Boulder March 1 and was kept under observation there until his death, April 29.

Clinical Course.—After a short period of seeming improvement, he underwent a series of attacks of acute rheumatism and complained of constant pain in the heart region. April 10 there was an attack of what seemed to be heart block with edema of the lungs, which soon cleared up. Attacks of the arthritis continued but seemed to be milder, and for a week previous to April 29 he was up in a wheel chair, being practically free from rheumatic pains. The day of his death there was a sharp attack of rheumatism accompanied by
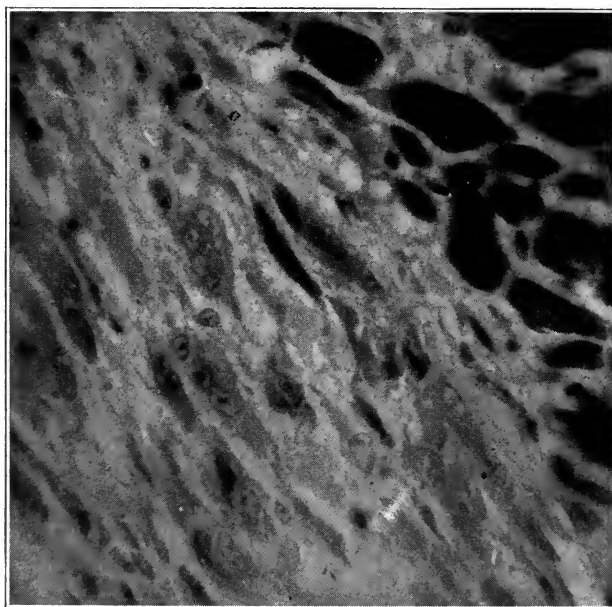

Fig. 3.—Field in a typical Aschoff body showing the epithelioid cells.

dyspnea, severe heart pains, orthopnea and pulmonary edema. The stethoscope revealed only two of the heart lesions found at necropsy, the mitral and the aortic.

ABSTRACT FROM THE NECROPSY PROTOCOL

The necropsy was held eighteen hours after death. There were no external signs except a very slight edema over the ankles. There were some fresh, easily separated adhesions over the left lung only. The lungs showed no areas of consolidation, but only slight crepitation, and on section and pressure yielded an abundant clear, frothy fluid. The heart was very large and the pericardium was closely and firmly adherent at all points. Mitral flaps were fused, thickened, rigid but not calcified, with a crescentic orifice and minute vegetations along the edge. The columnae carneae were shortened and fibrous. The aortic and tricuspid valves were similar to the mitral, while the pulmonary valve alone was normal. Left ventricle wall: 2 cm. thick; right ventricle wall: 12 (!) mm. thick.

Microscopic Examination.—The stains used were methylene-blue-eosin, methyl-green-pyronin, Mallory's iron-hematoxylin alone and in combination with eosin and with picric acid as counterstains. All illustrations were made from the iron-hematoxylin preparations as they showed the elements of the muscle cells the best. Regardless of the stain used, the cytoplasm of the type cells studied always stained the same shade and degree of intensity as did the cytoplasm of the muscle cells.

In every low power field there were from one to eight or ten nodules (Fig. 1) depending on the part of the ventricles examined. They were oftenest sub-endocardial and, as others have noted, it was found that, in order of the number of lesions, the papillary muscles come first, the left ventricle wall and the interventricular septum next, the right ventricular wall showing comparatively few lesions. Even with the low power it was plain that there were present lesions in all stages from the first sign of muscle cell necrosis with scarcely noticeable leukocytic infiltration to completely healed areas with quite dense scar tissue. The nodules, when recent, always were found around or near a
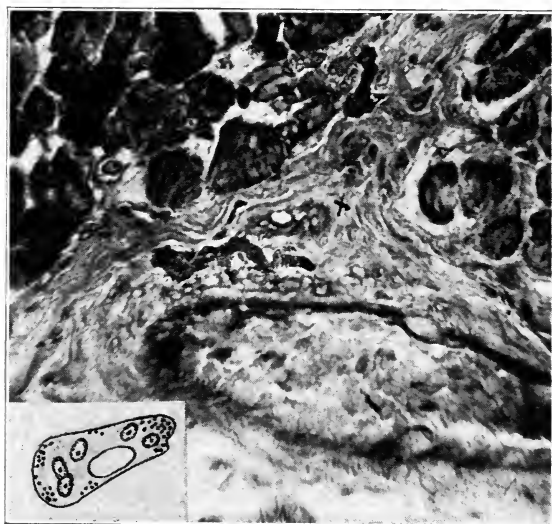

Fig. 4.—Late transitional stage from muscle to epithelioid cell. Inset is sketch of cell near center of picture.

small blood vessel, apparently, from its wall, an artery; or several such vessels may be found scattered here and there in a large nodule, possibly resulting from the confluence of several smaller ones.

DISCUSSION

The identification of the true Aschoff body was based on a study of its individual elements as demonstrated by the methylene-blue-eosin and the methyl-green-pyronin stains, and by its relation to the vessels. From the typical textbook types the lesions were traced back to the earliest demonstrable. In the present paper we shall confine our descriptions to the "large epithelioid cells," tracing them from the type found in the average Aschoff body through all stages to their earliest precursors.
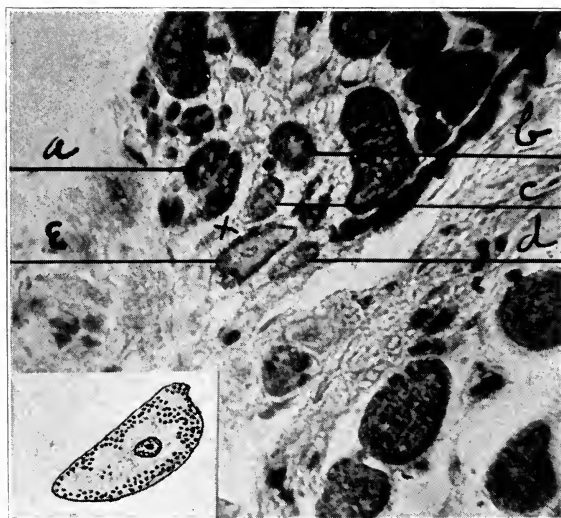
Fig. 5.—Early transitional stage from muscle to epithelioid cell. Inset is sketch of cell near center of picture.
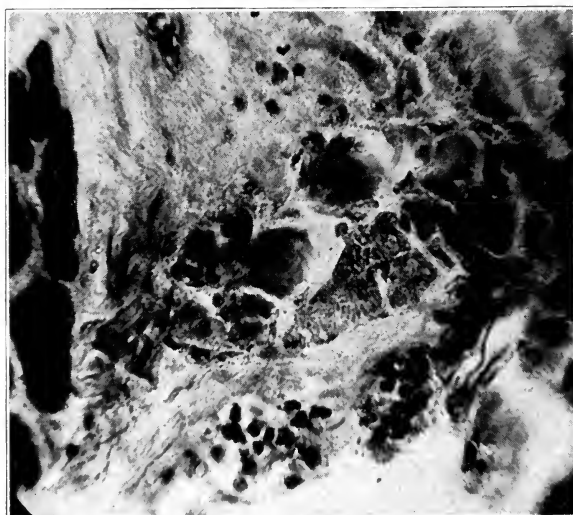

Fig. 6.—Separation of a muscle bundle into its components.

Figure 2 shows a field under higher magnification than in Figure 1, and cut in a different direction. This lesion is in a papillary muscle and at first was passed over as not being an Aschoff nodule. Closer study, however, revealed that it probably consists of several, at least four, confluent Aschoff bodies, a condition that, as far as we know, has not been reported before. The relation of the lesion to the muscle fibers is well shown, the latter seeming to break up and disappear in the lesion. At certain points (Fig. 2, a and b), the Aschoff cells are arranged in definite rows continuous with muscle fibers ending at the edge of the lesion as though the Aschoff cells originated by the fragmentation or attempts at regeneration of the muscle fibers.

In Figure 3 is shown the so-called "epithelioid cell" of the Aschoff body. There will be noted pear-shaped and elongated multinuclear cells with a fairly dark staining protoplasm. The cytoplasm is of even


Fig. 7.—Sketch of the central portion of Figure 6.

texture without more than the slightest suggestion of granules and no trace of fibrillae. The nuclei stain as a dark ring with a single dark nucleolus, in the center, target like, and number one to seven in each cell. These cells do not resemble fibroblasts, differing from them in their shape, size, reaction to stains, and number of nuclei. In the lesions studied there was usually ample opportunity to compare the two types of cells, since, when the lesion was at the stage exhibiting these cells, there were usually normal fibroblasts in good numbers in the same field with these abnormal cells.

Carrying the cell back through younger lesions we are able to show a clear series to the stage shown in Figure 4 where is seen a cell still showing evidences of being a muscle element. This cell has five nuclei and a rather large vacuole. The cytoplasm is colored the same as that of the cell discussed above and is otherwise identical with the epithelioid cell, except that there are a few striae at the poles of the cell consisting of small, deeply staining dots, a little larger and
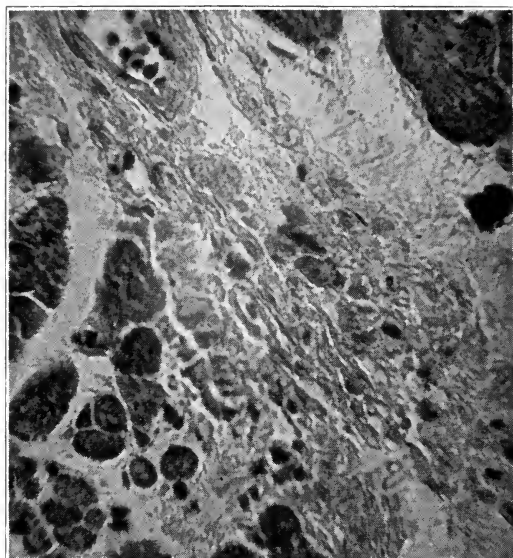
Fig. 8.—Healed lesion showing atypical muscle cells in the substance of the scar.
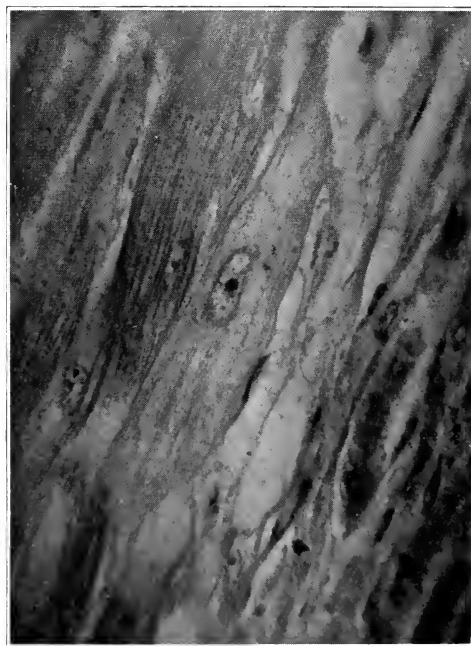
Fig. 9.—Transitional stage, long axis of the cell.

paler than those of normal muscle cells. The field used in the figure shows part of a rather young lesion.

It is but a few steps to the earlier stage shown in Figure 5. Each stage is well illustrated by many examples in many nodes. In this figure the photograph shows that the cell is a product of muscle cells. It clearly shows one nucleus in the center, the normal condition, and a border of striae represented by dots. That this cell is produced by separation of the cells of a muscle bundle into its constituent elements may be inferred from the appearance of such fields as shown in Figure 6, where a muscle bundle is shown in the process, but otherwise little changed from the normal, the striae being cut more obliquely than in Figure 5.


Fig. 10.—Sketch of the cell in the central part of Figure 9.

Referring again to Figure 5, the process by which the cell loses its striae is well illustrated. The cell marked *a* shows the earliest stage with the loss of only a few striae in the center of the cell, leaving a homogenous area. As shown in the other cells successively the process extends peripherally through the stage shown in Figure 4, where there are only a few striae at the cell poles with a decided proliferation of nuclei, to the stage illustrated in Figure 3.

It would be well to recall the way in which cardiac muscle cells acquire their fibrillae, since it is possible that the above mentioned cells should be regarded from another point of view. In the embryo the fibrillae appear first in the periphery of the cell and from there grow in toward the center. Therefore, it is possible that some of the cells studied may be the result of regeneration, rather than of degeneration. This is suggested by the statement of Geipel already quoted, and

by the appearance of such fields as are shown in Figure 8. This picture shows a healed Aschoff body in the center of which are several atypical but unmistakable muscle cells.

Not only do cross sections of the cells give a series from the "epithelioid type" to the unmistakable muscle cell, but the same is seen in sections depicting the long axis of the cell. Figure 9 shows under high magnification a rather large cell of a type intermediate between those of Figures 3 and 4. The cytoplasm takes the stains as preceding examples and contains a few rather indistinct fibrils, two of which clearly show cross striations and others give the suggestion of the presence of striae. As can be noted the cell is spindle shaped and about as wide as the adjacent nearly normal muscle cell. However,

Fig. 11.—Earlier transitional stage, long axis of the cell.

if it were not for the striae and the fact that some of the fibrillae seem to be continuous with those of more nearly normal muscle cells, one would hesitate to call the cell a muscle element. It is more like an Aschoff cell, and shows a clear resemblance to certain of the cells in such fields as illustrated in Figure 3. How such a cell arises is shown in Figure 11 by the cell with the two clear fibrillae, which show very clear cross striations. This cell was found lying deep in a nodule and very close to a vessel as is shown in the illustration, the dark wavy bands of connective tissue being from a vessel wall. The location, under low magnification, is indicated in Figure 2. Quite a number of such cells were found in various nodules studied.

Besides the typical Aschoff bodies, parts of which have been discussed above, there is present another type of lesion. These are areas of simple, early muscle-cell necrosis sometimes with early leuko-

cytic infiltration. Tracing one of these areas through serial sections, led to a small blood vessel occluded by an embolus, indicating that the area is an infarct in a quite early stage before the hemorrhagic zone was formed. Though we are unable to connect the oldest of these areas with the most recent of the identifiable Aschoff nodules because, perhaps, of the week's interval between the last two rheumatic attacks, mentioned in the case history, nevertheless, the idea presents itself that perhaps Aschoff nodules in their earliest stage, are very small infarcts.

We are not prepared to state that all of the "epithelioid cells" originate as above outlined, but it would seem from a careful study of such fields as have been depicted that many of the typical cells of typical Aschoff bodies are derived from muscle elements and that they have not been so described because of lack of such favorable material as was our good fortune to obtain. Further, it is our opinion that at least some of the Aschoff cells arise from muscle cells in two ways—through degeneration of existing elements and through regeneration. The bulk of the evidence points to the first of the two conclusions, but there is by no means little to make the second at least plausible. The case is exceptional. We do not know why such results could not be obtained experimentally, but an observation by Thalheimer and Rothschild [8] indicates that experimentally produced bodies are easily differentiated from true Aschoff bodies even when cultures from heart lesions are used.

<div style="text-align:center">CONCLUSIONS</div>

1. At least some Aschoff cells are derived from muscle cells.

2. In most cases the cell is the result of degeneration and proliferation of the nuclei.

3. In certain cases the presence of striae at the periphery of the cell suggests the possibility that the cell is a product of purely regenerative activity.

4. Certain facts in our case suggest the further possibility that the process may begin as minute infarct.

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8. Thalheimer and Rothschild: J. Exper. Med. **19**:429, 1914.

A STUDY OF THE LESIONS PRODUCED BY FILTRATES OF INFLUENZA SPUTUM *

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The hypothesis of a filtrable virus as the primary etiologic agent in epidemic influenza has been advanced by Nicolle and LeBailly,[1] von Angerer,[2] Bradford, Bashford and Wilson,[3] and by Gibson, Bowman and Connor.[4] The great diversity of bacteriologic findings in the disease would seem to render such a conception very attractive. It would appear very difficult to explain the epidemiologic characters of the disease on the assumption that it is primarily caused by any of the well known bacteria which have from time to time been associated with it, but which are also known to be present and active in the inter-epidemic periods. The clinical conception of influenza as a comparatively mild disease, characterized by a well marked toxemia and giving evidence of special predilection for the respiratory tract, and only dangerous, as a rule, when complicated by the so-called "secondary" pneumonia, from which a great variety of bacteria have been isolated, is also in harmony with the idea of an unknown primary cause. So, too, is the striking uniformity of the disease as observed in widely separated localities, irrespective of the fact that in one place one organism dominates the bacteriologic picture, and in another a totally different organism is found.

In spite of these elements of probability, the "filtrable virus" theory has not gained general acceptance, and the results of one group of investigators has been entirely discredited as far as their claims of cultivation of the organism are concerned.[5] The work of the men named, however, seems to confirm the claim that it is possible by the injection into experimental animals of filtrates of the sputum or blood of influenza patients to produce lesions of the lungs bearing some resemblance to those characterizing influenza, to cause the death of such animals occasionally, and to reproduce in other animals the same

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*From the Department Laboratory, Southern Department.

1. Nicolle, C. and LeBailly, C.: Compt. rend. Acad d. sc., **167**:607, 1918, and Ann. de l'Inst. Pasteur, **33**:395, 1919.

2. Von Angerer: München. med. Wchnschr., 1918, p. 1280.

3. Bradford, Bashford and Wilson: Quart. J. Med., **12**:88, 1918.

4. Gibson, H. G., Bowman, F. B., and Connor, J. I.: Brit. M. J., **2**:331, 1919; Spec. Rep. Med. Research Com. Brit. Nat. Health Ins., No. 36

5. Arkwright, J. A.: Brit. Med. J., **2**:233, 1919.

type of lesion by the further passage of filtered material. Whether or not the virus has been cultivated must for the present remain subjudice.

It occurred to me that light might be thrown on the subject by repeating the work in question with the idea of making a careful study of the lesions produced and comparing them with those accepted as characterizing the organs of patients dead of influenza. The return epidemic of January and February, 1920, at Fort Sam Houston, Texas, afforded an opportunity to obtain undoubted influenzal material and a series of experiments was inaugurated.

The general plan was to obtain a bacteriologically sterile filtrate of a sputum from an early severe case of influenza, to inject it into animals and to note results. Details of the technic employed will be given below. Results were considered positive only when the lungs of the infected animal showed microscopically a well marked lesion of the type subsequently described. The possibility that such lesions might be caused by a preformed toxin present in the patient's sputum has been borne in mind, and for this reason attention has been concentrated on the passage of the "virus" through a long series of animals rather than on the attempt to produce the lesions from a large number of cases of the disease.

Filtrates from the sputum in five cases of influenza have been used. In each instance positive results were obtained. In one case the gross lesion at necropsy was so slight that no further passage was attempted, although the microscopic findings were of a well marked and diffuse lesion of the same type as the others. A second strain was carried through two passages; a third through three passages with eight positive animals; a fourth through two passages with five positive animals; and a fifth through nine passages with twenty positive animals. In all, thirty-six animals, out of forty inoculated, have shown some degree of the process to be described; two were negative and two are still under observation.

The animals used have been rabbits, guinea-pigs and mice; inoculations were made intravenously, subcutaneously and in a few instances intraperitoneally. In each instance we have found the same type of lesion and all stages were noted. It is to be regretted that monkeys have not been available. Mice are, perhaps, the best animals for the purpose on account of convenience and the fact that it is oftener possible to give a lethal dose. This is probably not a matter of susceptibility but rather due to the fact that the dose employed is larger in proportion to the body weight. Owing to lack of space publication of detailed protocols of these experiments is impossible. An attempt will be made, however, to present the results with occasional references to especially interesting cases.

There has been no uniformity in the clinical symptoms observed after inoculation. Many animals have appeared to be in perfect health but when killed have shown marked lesions. When symptoms supervened, the period of incubation was extremely variable. In one rabbit (84 C) within twenty-four hours after inoculation the animal was extremely sick, refused food; its coat was rough; breathing was labored to such an extent as to suggest an obstructive condition in the air passages; temperature was elevated; death occurred in forty hours. Other rabbits showed no symptoms, except a slight loss of weight or in young animals a failure to gain as control animals of the same litter did. Temperature observations were negative in so many animals that they were discontinued later. Guinea-pigs showed no symptoms except a progressive loss of weight, in one case leading to the death of the animal after thirteen days. Mice were usually affected earlier. They showed a roughened coat, apathy and respiratory distress. The incubation period appears to be somewhat dependent on the effective dose administered, and there is at present no method of determining this factor.

The lesions found have varied greatly in degree but in kind they have shown prefect uniformity. The trachea has shown an inflammatory process characterized by hyperemia or hemorrhage in the intercartilaginous spaces so that the organ presented a marked "banded" appearance (Fig. 1). In many of the more severe cases the trachea and bronchi contained bloody froth or bloody mucus. The lungs did not collapse normally on removal from the thorax. There was in almost all cases some degree of dark red coloration on the surface of the lungs (Fig. 1). This varied in degree from the extreme represented by the rabbit mentioned that died in forty hours, in which practically the entire surface of the organ was a deep red color, to cases in which the only external sign was the presence of a few red spots a millimeter or two in diameter. In some instances the affected areas were sharply outlined, in others they were marked by a dusky red mottling with indistinct outlines. These doubtless represent different stages in the evolution of the process. Careful inspection of the surface of these lungs shows in most cases evidence of patches of emphysema. These are variously located, sometimes marginally, often between areas of the red coloration. Section of the affected organs shows in well marked cases the same general appearance as the surface. Areas dark red and denser than normal, usually sharply outlined from the lighter normal tissue, and areas of dilated vesicles are usually plainly to be seen. Portions cut from the dark areas float very low in water. In the more acute stages the cut surface is more moist than normal and may exude a bloody fluid or froth.

It has not been possible to show any relation of these lesions to the bronchi. With two exceptions the pleural surface has appeared unaltered. One of these was in a rabbit which showed a large empyema of the right side and a smaller accumulation of turbid fluid on the left side. The other was in a mouse infected with the filtrate of the lung of this animal which died after seventeen days and showed pleural adhesions and a small amount of a yellow fibrinous material in patches

Fig. 1.—Lung and trachea of rabbit 331. Tracheal banding, dark red spots and marginal emphysema are very evident.

over the right pleural surface. In both these animals the exudate was free from bacteria, as determined by careful examination of stained specimens and by culture.

The microscopic findings have been most uniform and characteristic. The lesion produced appears to begin as a marked hyperemia of the alveolar tissue of the lung. The lung in this stage looks as

if the capillaries had been injected, so plainly do they outline the walls of the air spaces. The alveoli are empty or contain large mononuclear cells and sometimes a few erythrocytes. This condition is not uniform throughout but occurs in irregularly distributed areas separated by normal tissue. Necrosis of the capillary walls, as evidenced by disappearance or fragmentation of the endothelial cells, is seen in some places. In more advanced cases the characteristic lesion of the condition is fully developed. This consists of hemorrhage into the walls of the alveoli with disappearance of the original capillaries. The resultant thickening of the walls encroaches on the air spaces to a
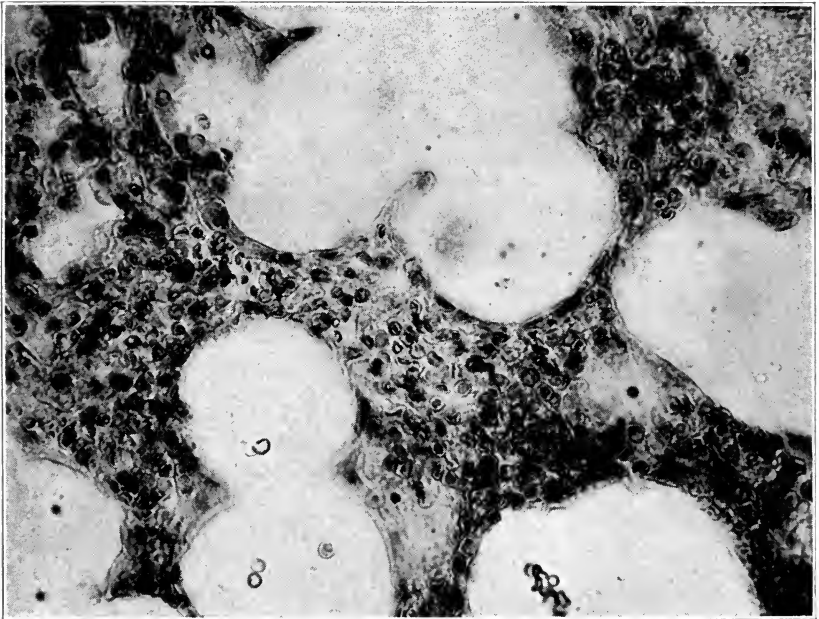
Fig. 2.—High power view of lung of mouse 2. Shows interstitial character of hemorrhage.

varying extent, often to the point of obliteration, so that such an area becomes consolidated almost completely, showing only here and there a small round vesicle that still contains air. The margins of such an area show the alveolar structure persisting but with greatly thickened walls (Fig. 2). The unaffected tissue about such an area is composed of greatly dilated infundibula with thin walls. The hemorrhage can be shown to be distinctly interstitial in character by the persistence in many cases of the lining epithelium of the air spaces (Fig. 2). In this stage the bronchi show desquamation of

their epithelium and frequently contain red blood cells (Fig. 3). There is a notable absence of any infiltration by polymorphonuclear leukocytes.

A slightly later stage of the process shows the breaking down or lysis of the erythrocytes in the alveolar walls. This can be traced from well preserved cells through gradual diminution of distinctness of outline and intensity of stain to a stage in which shadows only of the cells are seen, and finally only a hyalin eosin staining substance remains.

In this process the pigment of the cells is liberated and is seen free in the walls and also to a great extent taken up by large mononu-
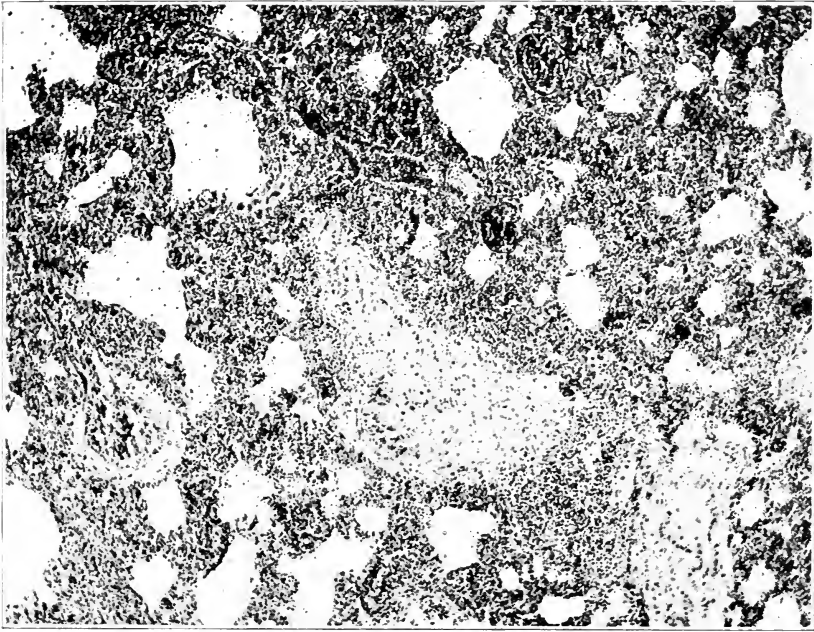
Fig. 3.—Low power view of lung of rabbit 84 C. Shows diffuse interstitial hemorrhage, and occlusion of bronchi by desquamated epithelium.

clear cells, perhaps endothelial leukocytes. Parallel with this process is the appearance in the thickened walls of an increasing number of mononuclear elements of various sizes. Some seem to be lymphocytes, others with oval vesicular nuclei suggest young connective tissue cells. Polymorphonuclear cells are not seen. The compressed air spaces during this stage may contain the same cellular elements as earlier, but in addition, in some part of almost every section, there is seen lining the alveoli a hyalin substance which appears to be closely adherent to the alveolar walls (Figs. 4 and 5). Some alveoli may be filled completely by it, others still contain one or more bubbles of air. The

usual condition, however, is to find a layer coating the wall. The condition suggests the exudation into the alveoli of a viscous, tenacious semifluid substance which takes its form from that of the vesicle containing it under the influence of the respiratory movement of air. This substance does not give the reaction of fibrin with the Weigert stain. It is usually stained faintly with eosin but in eosin-methylene blue preparations it is slow to give up the blue and unless differentiation is carried to completion it retains the blue color.

This substance differs from an ordinary edema fluid in its hyalin appearance and in its distribution. In fixed preparations coagulated
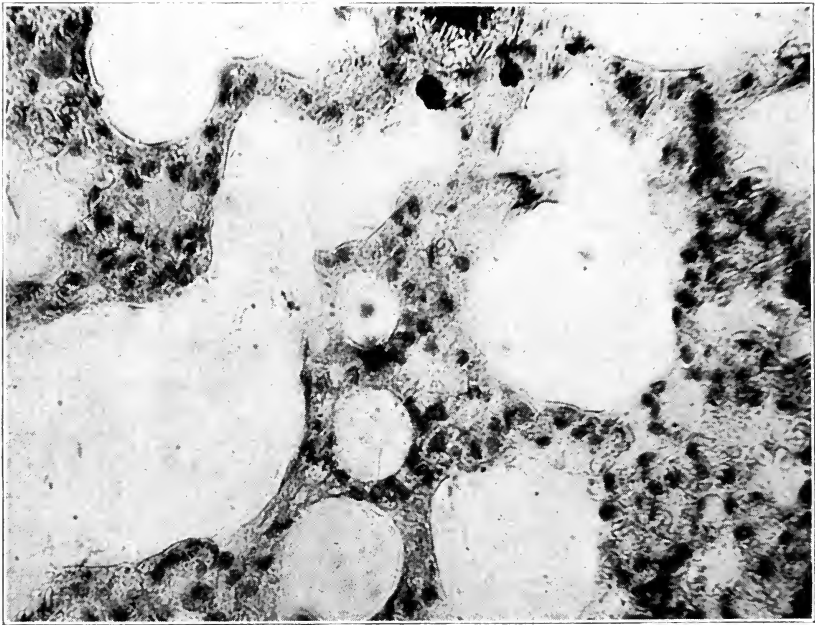
Fig. 4.—High power view of lung of rabbit 396. Shows infiltration of thickened alveolar walls by mononuclear cells, and deposit of hyalin membrane in alveoli.

edema fluid usually shows as a somewhat contracted cast of the alveolus, separated from the walls. This hyalin material is always closely applied to the wall of which it appears to be a part. Its origin is not clear, but certain sections have suggested that it may represent altered blood, exuded as such into the alveoli, there to undergo the same lytic change as already described for the blood in the alveolar walls. We have been able to trace the process with some distinctness through the gradual disintegration or disappearance of the red cells to the hyalin substance as described. In sections of this stage of the process the bronchi are often plugged completely with desquamated

epithelium, red cells and granular detritus. There is a notable increase of the peribronchial adenoid tissue, and focal accumulations of lymphoid cells occur about the larger blood vessels (Fig. 6). Occasionally, such a focus appears to be unrelated to bronchus or vessel. Several times we have observed the infiltration of the bronchial mucosa by these small round cells which penetrate the muscularis and lie between the columnar epithelium or in some cases displace the epithelium with the formation of small ulcers. The lymphatics throughout the section are enormously dilated and contain a hyalin substance similar to that found in the air cells with a few lymphocytes. When
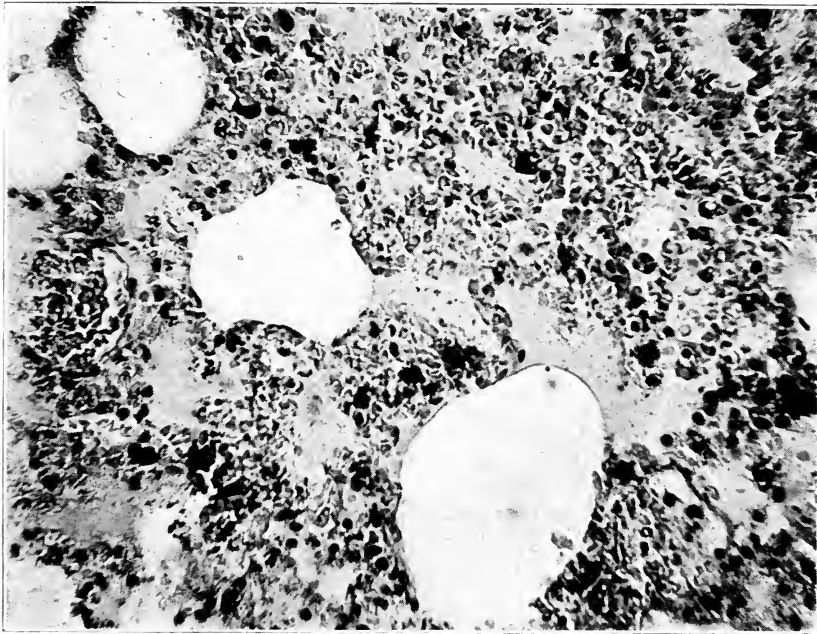
Fig. 5.—High power view of lung of rabbit F. Shows hemorrhage, interstitial and intra-alveolar, deposit of pigment, catarrhal exudation and presence of hyalin substance in alveoli.

pigment is present in the alveolar walls, the majority of specimens show the presence of eosinophil cells, usually mononuclear.

In cases that showed a superficial area of red coloration extending a short distance into the parenchyma of the lung, the microscope shows this to be due to an area of atelectasis doubtless caused by the obliteration or plugging of the bronchus supplying the area. The actual lesion itself is not apt to be subpleural, though these areas of atelectasis frequently give that impression in the gross.

In a few instances the hemorrhagic tendency has been so marked that the blood has escaped at once into the alveoli instead of being

confined to their walls. In such cases, however, the margins of the affected area show the usual interstitial arrangement in a way similar to the corresponding stages of pneumococcus infection, as shown by Blake and Cecil.[5a] Another interesting condition is the presence in many cases of thrombi of hyalin material in good sized blood vessels. In these, as well as in the alveolar walls, and in the air spaces, it has seemed possible to trace the transformation of blood to the hyalin substance through the intermediate stages.

Aside from blood and the hyalin substance the alveoli showed no marked exudate in most cases. In the more severe cases, however,
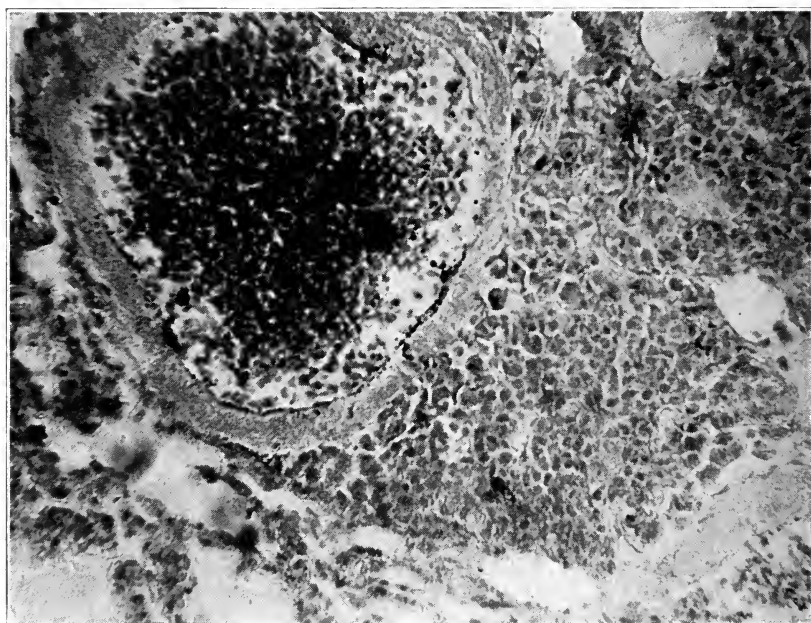
Fig. 6.—High power view of lung of rabbit 388. Shows blood vessel with hyalin degeneration of media and focus of lymphoid cells.

numbers of large mononuclear cells were present in most alveoli. These had the appearance of swollen and desquamated epithelium. In one fatal case large areas of the lung showed the alveoli filled with cells of this type so that at first glance it resembled gray hepatization. The intervening alveoli were completely filled with blood. Edema has been a rare finding. In one or two cases, however, it has been present. Fibrinous exudation in the alveoli has not been observed. In the two cases showing pleuritis fibrin was present in the exudate

5a. Blake, F. C., and Cecil, R. L.: J. Exper. M. **31**:445, 1920.

in small amount. Polymorphonuclear cells were also present in the pleuritic exudate with about an equal number of mononuclear cells.

The further evolution of the process is one of organization of the hemorrhagic areas. The number of nucleated elements in the thickened alveolar walls increases, the eosin-staining matrix resulting from the lysis of the red cells disappears, pigment is no longer seen and ultimately the areas are converted into scarlike connective tissue which still, however, shows the form of the thickened alveolar walls with alveolar spaces of reduced size (Fig. 7). Blood vessels and bronchi involved in this formation are compressed and atrophic. The nodular
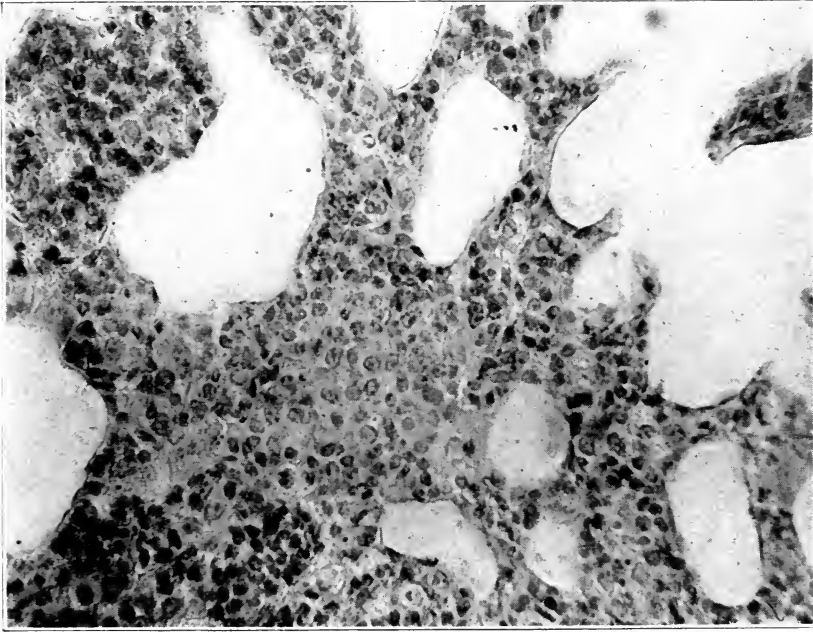
Fig. 7.—High power view of lung of guinea-pig 7. Shows carnification of thickened alveolar walls.

accumulations of lymphoid cells are no longer seen. The intervening lung tissue is even more expanded and emphysematous than was the case in the acute stages.

In organs other than the lungs, the same tendency to congestion and hemorrhage is found, and in addition, in parenchymatous organs, degeneration of epithelium. Except in the lung, lymphoid infiltration is rare.

The liver has usually been dark in color and dripped blood on section. Such organs showed microscopically dilatation of their blood vessels, usually most marked in the capillaries. In some cases a yellow

mottling of the surface was seen which was due to fatty change in the cells. Still other cases showed in addition to the congestion an extreme degenerative change in the liver cells. There was a transformation of the cytoplasm into coarsely granular material, and later its disappearance so that in the most advanced cases the cell consists of a membrane containing a well preserved nucleus, but apparently without cytoplasm. Focal necroses were not observed, except in cases showing secondary infection.

In the kidney a similar change was seen in the cells of the convoluted tubules. They were swollen and granular and occluded the lumen and especially under the capsule the cells were disintegrated, though never to the extent observed in the liver. Intertubular edema, marked cortical congestion and sometimes hemorrhage, were frequent findings. In one case intertubular infiltrations with lymphoid cells were found. The glomeruli were frequently somewhat contracted and the capsular epithelium swollen, in some cases distinctly cuboidal. Tubules and capsule often contained granular precipitate.

The spleen in early cases was usually large, soft and pulpy. The malpighian bodies were well preserved but the remainder of the organ was intensely hyperemic or hemorrhagic with blood pigment often present. Spleens from later cases were smaller and harder; the lymphoid elements of the pulp were much reduced and replaced by large mononuclear cells and fibroblasts.

The bronchial lymph nodes were regularly enlarged and dark red in color. Microscopically, they showed congestion and dilatation of the blood channels with widening of the marginal sinuses which frequently contained red blood cells. In animals injected subcutaneously the regional lymph nodes at the point of injection showed marked changes of the same character.

The brains of a few animals were examined and showed congestion and occasionally perivascular hemorrhage but no leukocytic infiltration.

The testes showed degenerative changes, loosening and separation of the cells of the tubules and in some cases cessation of spermatogenesis. In all organs hyalin degeneration of the walls of blood vessels is occasionally seen.

The essential feature of the process appears to be an injury of the walls of the blood vessels, especially the capillaries, evidenced by congestion and leading to hemorrhage. In the lungs this process is primarily interstitial or limited by the lining membrane of the alveoli, except in cases of exceptional severity when the blood is freed into the air spaces. There is no evidence of polymorphonuclear reaction, and except in cases of secondary infection purulent exudates do not

occur. Lymphoid infiltration is conspicuous in some stages of the process. This occurs in the thickened walls of the alveoli with the disappearance of the red cells, is frequent about the larger blood vessels and the normal peribronchial adenoid tissue is often increased and may infiltrate and even destroy portions of the bronchial mucous membrane. The secondary changes in the hemorrhagic exudate are of interest. The cells undergo lysis, passing first into a "shadow" stage and later into a hyalin eosin-staining mass. This process may give the explanation of the hyalin membrane lining the alveoli which is frequently observed. It may also account for the frequent finding of hyalin thrombi in the blood vessels. The hemorrhagic tendency is not limited to the lungs as hemorrhage has been seen in the liver, kidney, spleen, brain and voluntary muscle. The liver and kidney also show marked parenchymatous degeneration.

CONTROL EXPERIMENTS

The sputum from five different patients with noninfluenzal conditions was injected into twelve animals. These experiments were consistently negative and failed to show any lesions in any way resembling those described. The cases selected were of acute and chronic pulmonary and bronchial affections sent to the laboratory for examination for tubercle bacilli. This work was not done until two months after the height of the epidemic as it was felt that during the prevalence of the influenza it would be impossible to feel assured that the sputum did not contain the infective agent even in the absence of symptoms.

That the lesions are not produced by the injection of lung extracts is shown by one experiment in which the lung of a normal rabbit was emulsified, filtered and injected into a rabbit and a guinea-pig with negative results. That anaphylaxis or specific cytolysins might enter into the matter seemed possible, but at no time in the passage experiments has the lung extract of one animal been injected into one of another species and the lung of the latter injected into a member of the former species. The continuance of the process through nine animal passages would effectually rule out the possibility of a soluble toxin in the original sputum being responsible for the changes.

The attempt was made three times to control the injections by heating the portion of lung emulsion injected into one of the animals. Once the filtrate was boiled momentarily, once heated for two hours at 56 C. and once for one-half hour at the same temperature. All three of these cases showed positive lungs at the necropsy. It would thus appear that the agent responsible for the changes is not easily destroyed by heat.

TECHNIC

Sputum was collected in sterile containers from early cases of apparent severity. Microscopic examination in all cases showed the presence of a variety of organisms including pneumococci, streptococci, and small gram-negative bacilli. No attempt was made to isolate the various bacteria observed. The sputum was ground with sand in a sterile mortar diluted with several volumes of 0.85 per cent. saline solution and filtered through a Berkefeld or Mandler filter. The filters used were in all cases previously tested for their ability to retain the Pfeiffer bacillus and were shown to be in good condition. The filtrates were in every case cultured before injection into animals. The medium used for this purpose was the heated horse blood agar successfully used in the laboratory in the cultivation of the Pfeiffer bacillus, and which is also a good substrate

for the growth of all the known bacteria usually affecting the lung. In all cases these cultures remained sterile after a week's incubation. In several of the earlier experiments cultures were also kept under anaerobic conditions with like results.

Filtration was done directly into a plugged test tube which was sterilized with the filter and only opened after filtration, when a fresh sterile plug was at once inserted. Filters and tubes were sterilized in the autoclave under fifteen pounds pressure for thirty minutes. Filtration was always started under a negative pressure of not more than fifty millimeters of mercury. The filters usually clogged to some extent very quickly and more pressure was used in most cases before the necessary amount passed through. The rate of filtration never exceeded ten or fifteen drops per minute and was often much slower than that.

Needles and syringes used for injections were freshly boiled. Injections were made intravenously and subcutaneously in rabbits, subcutaneously in guinea-pigs and mice. In killing animals for examination, every care was taken to avoid any injury to the lungs. The best method is, perhaps, a blow in the cervical region producing immediate death. However, chloroform does not appear to alter the picture in any way.

In dissecting the animals the trachea was first exposed and clamped in order to avoid the possibility of entry of blood from severed vessels.

The lungs of affected animals were cut into small pieces after examination, grouped in a sterile mortar, the pasty mass suspended in saline solution, centrifugated lightly and filtered with the same precautions as were used for the sputum. In every case the filtrate was tested for sterility by culture methods before injection and was in every case sterile as far as that method is capable of determining.

Except in the cases noted otherwise, the lungs of all these animals were negative bacteriologically when examined. The heated horse blood agar was used as a routine medium for this purpose also.

Tissues for microscopic examination were fixed in 10 per cent. liquor formaldehydi or in Zenker's fluid and stained with hematoxylin and eosin, methylene blue, eosin and for bacteria with the McCallum-Goodpasture stain.

DISCUSSION

We have been able to produce in the animals used pulmonary lesions of a uniform type by injections of bacteriologically sterile filtrates from the sputum of five patients actually ill with influenza. A like number of experiments identically conducted but using sputum from patients in whom influenza could be excluded were entirely negative. We have been able to produce the same type of lesion in other animals by the injection of bacteriologically sterile filtrates of emulsions of the lungs of the animals first affected. This process can apparently be continued indefinitely. In view of these results, it seems justified to assume that we have been dealing with a living organism or virus, capable of passing through the filters used, which gives no visible growth on the culture medium employed, and which is able to induce in animals lesions of the type described. That these lesions were formed by a preformed toxin present in the patient's sputum seems definitely excluded in view of the passage through a long series of animals. The lesion is not the result of the injection of lung extract as is shown by the injection of filtered emulsions of the lungs of

normal animals as well as the occasional occurrence of negative results in our series. Experiments in cultivation of this "virus" have led us as yet to no definite conclusions, and until it is cultivated it is not possible to satisfy Koch's requirements for the demonstration of the relation of the organism to the disease.

If, however, it can be shown that the lesions developed in the course of this work can be harmonized with those accepted as characterizing the organs of patients dead of influenza, it would appear to be confirmatory of the claims of those writers who have advanced the "filtrable virus" as the primary cause of the disease. To obtain a basis of comparison it is necessary to consider the fact that in fatal cases of influenza in man there is present almost invariably infection with one or the other of the well known bacteria which have for years been associated with pulmonary inflammations in the absence of influenza. In one locality one form is found almost to the exclusion of others; in another locality a totally different form is found. This must be admitted in spite of the facile assumption of some authorities that failure to isolate the Pfeiffer bacillus has been due to the use of improper technic. It is natural, then, that the pathology, gross and microscopic, as described by different observers should vary to a considerable extent. Two methods appear available for determining the essential characters of the influenza lung. One method is to correlate the findings that are common to all groups of cases reported during the epidemic, irrespective of the organism reported as present, or the points in which such lesions differ from those usually produced by the same organism; the other method is to determine the findings that characterize those fulminant early cases which end in death before secondary infection could be much of a factor; those cases that failed to show bacteria on lung culture, or in which the bacteria, if present, were shown to be in such small numbers as to raise some doubt as to their relation to the process.

Reference to the recent literature gives sufficient data from cases of these classes to enable one to form a fairly comprehensive picture of the essential lesions of the primary influenza infection. One of the most comprehensive recent accounts of the pathology of influenza is contained in the study of a large series of necropsies at Camp Zachary Taylor during the 1918 epidemic, by Lucke, Wight and Kime.[6] They classified their cases into different types and found one type predominating in the early days of the epidemic and in those cases that ended in death after a relatively short illness, and they advance the view that this type represents most nearly the lesions of the primary virus. This type of lung is characterized by dark red or

6. Lucke, Wight and Kime: Arch. Int. Med., **24**:154 (Aug) 1919.

purplish mottling externally, the anterior edges of the lung frequently being emphysematous. The upper lobes are involved as frequently as lower. The cut section is dark, moist and exudes a bloody fluid. Areas of consolidation blend into the surrounding tissue rather than being sharply marked. Microscopically, hyperemia, hemorrhage and catarrhal exudation are the outstanding features. The capillaries are hugely dilated and frequently contain conglutination thrombi. The exudate is catarrhal with admixture of a large proportion of red cells. Polymorphonuclear cells are rare. There is desquamative bronchitis and bronchiolitis. Hyalin or conglutinative thrombi are found even in good sized vessels. In older cases evidence of carnification is seen. The trachea shows a hemorrhagic inflammation in these cases and usually contains bloody froth. The pleura is frequently involved in fatal cases, the exudation being of all types from serous to purulent. Cytologically, the pleural exudate contains large mononuclear cells, with an admixture of polymorphonuclears. All observers agree that hemorrhage is a marked and early feature. Goodpasture and Burnett [7] say: "Primary toxic injury to the pulmonary tissue is a constant feature in the early stages of the pneumonia and presents a fairly characteristic picture. Alveolar walls are injured, capillaries ruptured and in places necrosed; there is an exudation of all the elements of the blood, larger or smaller areas of hemorrhage. Leukocytes are not especially prominent at this time and many are of the large mononuclear variety; and at this stage, organisms are comparatively few within the alveoli." They assume that the marked changes found in the lungs with so few bacteria are due to the toxin elaborated by bacteria in the upper air passages. This finding is, of course, as well explained by the assumption of an invisible infecting agent.

In speaking of early cases Wolbach [8] says: "the lungs are partially collapsed, dark red, lax but meaty in consistence. The pleural surfaces are often partly covered with dusky red mottling, due to small extravasations of blood beneath the pleural coat, . . . on section the lungs are dark red and wet, . . . on close inspection the surfaces are usually found to be thickly sprinkled with air vesicles of considerable size." Of the microscopic findings Wolbach says that the distinctive feature is an "acute alveolar emphysema, with the deposit of a hyalin fibrinous substance on the alveolar walls, the intervening alveoli are compressed and filled with exudate, which in the early stages is largely serous or bloody." The hyalin fibrin "outlines cavities filled with air which may or may not completely fill groups

7. Goodpasture, E. W. and Burnett, F. L.: U. S. Naval Med. Bull., **2**:177, 1919.

8. Wolbach, S. B.: Bull. Johns Hopkins Hosp., **30**:104, 1919.

of alveoli." While Wolbach does not mention the interstitial character of the hemorrhage in these early cases, his Figure 5, "a low power photomicrograph from an uncomplicated early influenza pneumonia," suggests very strongly this type of lesion.

Lecount [9] emphasizes the hemorrhagic character of the condition and draws special attention to the necrosis of the pulmonary capillaries. Oberndorfer [10] found marked hemorrhagic infiltration and later catarrhal or purulent exudate. W. G. McCallum [11] reports that the lesions found in early cases and especially in those showing the Pfeiffer bacillus on culture, suggest those described by him in the postmeasles pneumonias of the winter of 1917-1918 in army camps. (In this connection it is interesting to note, in passing, that many of these cases showed no history of recent measles and that Howard and Love [12] have expressed the opinion based on a study of the army statistics for 1917 and early 1918 that we had influenza with us in a mild form for more than a year before it assumed epidemic proportions). The distinctive feature of the postmeasles pneumonia as shown by McCallum was the interstitial location of the lesion. In the influenza cases he, too, has noted the hyalin substance lining the alveolar walls, and says that it does not give the reactions of fibrin. All these observers note a tendency to healing by organization which is seen even in fatal cases. P. J. Walker [13] describes the pathology of influenza, independently of the organism found in culture as "primarily an acute hemorrhagic lesion, interstitial or massive in extent."

It would appear, then, that the essential pathology of the influenza lung, unmodified by secondary infection, consists in an injury to the capillary walls resulting in congestion and hemorrhage, frequently interstitial, with obliteration or compression of some alveoli and emphysematous dilatation of others, leading in severe cases to intra-alveolar exudation of blood or serum, with little, if any, reaction on the part of the polymorphonuclear leukocytes, and with a tendency to healing by organization. There is described a characteristic hyalin membrane coating the walls of the alveoli in the neighborhood of the hemorrhagic lesions and in some cases completely filling the alveoli. Catarrhal exudation in alveoli, and especially in the bronchi, is described. Interstitial cellular reaction would appear to be lymphocytic. There is a rather constant hemorrhagic inflammation of the trachea. Other changes appear to depend on the presence and activity of various secondary invaders and to vary somewhat with the organisms found.

9. Lecount, E. R.: J. A. M. A., **72**:650 (March 1) 1919.
10. Oberndorfer: Münch. med. Wchnschr., **65**:810. 1918.
11. McCallum, W. G.: J. A. M. A., **72**:720 (March 8) 1919.
12. Howard, D. C., and Love, A. G.: Mil. Surg. **46**:522, 1920.
13. Walker, O. J.: J. Lab. & Clin. Med., **5**:154, 1919.

A comparison of the process found in our animals with the summary of findings in influenza as deduced from the published reports leads easily to the conclusion that the two are essentially similar, if not identical. The character of the lung lesion is the same in its primarily hemorrhagic nature, in its frequently interstitial location, in the absence of polymorphonuclear reaction, in the presence to some degree of catarrhal exudation in the alveoli and to a marked degree in the bronchi, in the presence of the hyalin membrane and of intervening emphysema and in the tendency to a final stage of carnification. The tracheitis is common to both conditions. Of lesions of other organs found more or less constantly in our cases, the type of kidney change agrees well with that described by Lucke, Wight and Kime, as does the finding in the spleen, large and congested in the earlier cases, atrophic with deposit of pigment and the presence of large mononuclear cells in the later stages. We have one instance of empyema in a chronic case and one dry pleurisy in a case ending in early death. We have one instance of hemorrhage in a degenerated voluntary muscle.

That the lesions found may be modified by secondary infection in such a way as to produce a picture even more similar to that of the usual influenza lung is shown by the results in certain mice in which material contaminated with *B. aertrycke* was used. Mouse 1 was inoculated intraperitoneally with the lung filtrate of a rabbit, the fourth passage from the original sputum. After four days of illness the mouse was killed and examined. The lungs showed the familiar interstitial hemorrhagic lesion. Further passages from the lungs were also positive. The peritoneum was washed and the washings centrifugated at high speed for ten minutes. The supernatant fluid was injected into a mouse and produced hyperemia of the lung but no characteristic lesion. The sediment suspended in saline solution, injected intraperitoneally, killed the mouse in eleven days, the lungs showing interstitial hemorrhage, but in most places so masked by infiltration with large numbers of polymorphonuclear leukocytes that the hemorrhagic character was only recognizable in scattered areas. Both lung and peritoneum showed cultures of *B. aertrycke*. Unfiltered peritoneal washings from this animal injected subcutaneously into two more mice produced death promptly. One mouse which died after fifty hours showed a condititon comparable to that last described. The other mouse, succumbing after only thirty-six hours showed a marked hemorrhagic lesion of the usual type without polymorphonuclear infiltration. This animal seems to have died of the primary infection before secondary infection developed and is comparable to certain fulminant cases of influenza. The fact that *B. aertrycke* ordinarily shows no tendency to produce pneumonic lesions indicates that in these cases the primary infection had prepared the way for the bacillus, which at necropsy

would appear to have caused the interstitial pneumonia. The filtrate of the lung emulsion of this animal proved capable of continuing the passage of the original lesion.

After the completion of the work here recorded, Olitsky and Gates published a preliminary note [14] of work which in many ways parallels ours with apparently harmonious results. Their short description of lesions produced would appear to differ from those here described not more than the difference in method of inoculation could easily account for. Our results appear to show that the infecting material injected into the circulation has a special predilection for pulmonary tissue but is also able to produce similar lesions in other organs. While the bronchial route is the most probable one for infection in nature, we have no definite proof that such is the case, and it is interesting to show that the "virus" locates in the lungs selectively when introduced into the circulation.

CONCLUSIONS

1. It is possible, by the injection of bacteriologically sterile filtrates of sputum from early cases of influenza into the circulation to produce in animals lesions of a uniform type uncomplicated by the presence of demonstrable bacteria.

2. The lesions thus produced are characterized by hemorrhage, a peculiar lytic change in the effused blood resulting in a hyalin end product with the deposit of pigment, infiltration by small mononuclear cells and eosinophils and healing by carnification.

3. These changes are comparable to those reported by many observers as characterizing influenza in so far as primary lesions may be separated from those produced by secondary invaders.

4. Control experiments with noninfluenzal sputum and with extract of normal lung are negative.

5. By injection of filtrates of lung emulsion from infected animals, the same lesion can be produced in other animals and the passage apparently continued indefinitely.

6. These results seem to give support to the theory of a filtrable agent as the primary cause of influenza.

7. Certain experiments indicate that the active agent concerned is markedly resistant to heat, and probably is mainly intracellular in location.

14. Olitsky, P. K., and Gates, F. L.: J. A. M. A., **74**:1497 (May 29) 1920.

CHRONIC BRADYCARDIA *

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Chronic bradycardia and its attendant cardiovascular phenomena present innumerable interesting problems. Many causes are ascribed to the slow heart; this results in a cumbersome and confusing classification. It may not be amiss briefly to summarize the causes generally accepted:

1. *Chemical Substances.*—The inhibitory action of the following substances is well known and warrants no discussion here: (a) The neutral non-nitrogenous glucosids and resins; the active principles of digitalis, squills, strophanthus and apocynum; (b) alkaloids such as erythrophlein, veratrin and aconitin; (c) biliary constituents, and (d) inorganic substances, such as barium salts and hydrates.[1]

2. *Stimulation of the Cardiac Vagus.*—Stimulation may be peripheral or central.

3. *Myocardial Disease.*—Involvement of the myocardium by disease (a) associated with lesions of the auriculoventricular bundle (complete heart block and delayed impulse transmission), and (b) without involvement of the bundle.

4. Certain physiologic reactions without cardiac damage.

5. *The early and late stages of asphyxia.*[2]

PHYSIOLOGY OF CHRONIC BRADYCARDIA

Slowing of the heart may occur (1) through stimulation of the cardiac vagus, and (2) through changes affecting the cardiovascular system independent of innervation influences.

Vagus Stimulation.—Stimulation of the vagus may be peripheral or central. The cardiac effect is four-fold: (1) the inhibitory influence slowing rate (negative chronotropy); (2) the diminishing strength of contraction (negative inotropy); (3) the diminishing irritability (negative bathmotropy), and (4) the diminishing conductivity (negative dromatropy).[3] Bradycardia resulting from vagus influences is not permanent.

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* From Section on Medicine, Mayo Clinic.

1. Sollmann, T.: A Text-Book of Pharmacology, Philadelphia, W. B. Saunders Company, 1908, p. 477.

2. Konow, H. G. and Stenbeck, T.: Ueber die Erscheinungen des Blutdruckes bei Erstickung, Skand. Arch. f. Physiol., 1:403, 1889. Quoted by Hirschfelder, p. 38.

3. Eppinger, H. and Hess, L.: Vagotonia. A Clinical Study in Vegetative Neurology. Nervous and Mental Disease Monograph Series No. 20. New York, Nervous and Mental Disease Publishing Co., 1915, pp. 14-15.

Changes Affecting the Cardiovascular System Independent of Innervation Influences.—The degree of cardiac filling and hence the volume outflow for each beat is directly modified by rate. Filling occurs during diastole and therefore the duration of diastole which is determined by rate, directly influences the volume outflow of blood.

The diastolic period is divided into two parts: (1) diastole proper, during which the filling of the ventricles is effected, and (2) diastasis, the period during which little or no filling occurs. "The greatest amount of output in unit time occurs at a rate which just allows the phase of diastolic filling to be complete but in which the next beat occurs before diastasis sets in. Any rate above or below this brings about some slowing of the circulation." [4]

Slowing of the heart rate below the point where adequate circulation is maintained due to diminished volume outflow per each beat as affected by rate, is cared for by other factors. An early attempt to increase volume outflow is by increasing contraction amplitude. This is not only revealed in the cardiac mechanism, but also in the effect on the general circulation. These circulatory phenomena are found in blood pressure studies, in the elevation of pulse pressure beyond normal limits. [5] The increase of pulse pressure is due largely to elevation of the systolic blood pressure. This cardiovascular status predisposes to ventricular hypertrophy, particularly of the left ventricle, another factor favoring increased volume outflow.

The systolic pressure represents essentially the strength of the heart beat. Its elevation, provided rate remains low and peripheral resistance constant, means complete ventricular filling and the subsequent expulsion of a large mass of blood. The diastolic pressure, other factors remaining constant, indicates the degree of peripheral resistance. It is logical, therefore, to argue that with the rate remaining low, the peripheral resistance remaining constant, the systolic pressure elevated and the diastolic pressure remaining normal, the increased pulse pressure represents increased volume outflow of blood. Add to these events an increased peripheral resistance and one of several phenomena results:

1. The heart rate remaining slow, a marked increase in both systolic and diastolic pressures occurs, resulting in a large pulse pressure. The degree of this reaction depends on the heart rate and the degree of peripheral resistance. This reaction is indicative of an increased volume outflow of blood.

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4. Hirschfelder, A. D.: Diseases of the Heart and Aorta. Philadelphia, J. B. Lippincott & Co., 1918, p. 11.

5. Plummer, H. S.: Personal Communication.

2. The heart rate accelerating and elevation of systolic pressure and greater elevation of diastolic pressure with a relatively smaller pulse pressure than in the preceding reaction is also evidence of increased volume outflow. In this instance the increased volume outflow is effected not only by increased amplitude of contraction but also by increased frequency of contraction.

When contraction amplitude diminishes, the rate accelerates and both systolic and diastolic pressures fall with diminution in pulse pressure. This phenomenon occurs when myocardial disintegration supervenes and as heart failure begins several additional factors come into play. With circulatory failure slowing of the circulation occurs, and there is a tendency to increase venous pressure which favors cardiac overdistention, predisposing to dilatation. This results in an increased carbon dioxid blood content which diminishes the tonicity of the heart muscle [6] thus further favoring dilatation. Cardiac dilatation implies diminished contraction amplitude, resulting in rate acceleration in the attempt to maintain adequate circulation.

Thus far my discussion has involved only the secondary effects of a primary bradycardia. Primary alterations of cardiovascular balance producing secondary bradycardia will be considered.

A cardiovascular system which has been subjected to increased demand for a relatively long period becomes an over-efficient mechanism when the demand is decreased. This statement must be modified in definitely excluding myocardial disintegration. Hypertrophy of the left ventricle is usually evident.

As circulatory demand is lowered, volume outflow is controlled by cardiac slowing also accompanied by circulatory changes. Pulse pressure is increased again by elevation of the systolic pressure.

These phenomena are observed in the over-efficient heart of the athlete after he assumes sedentary life, in certain cases of hyperthyroidism after the basal metabolic rate has attained normal and after the return to normal of a hypertension maintained for a time. Again, I wish to exclude the element of heart failure.

Another physiologic reaction often attended by bradycardia is observed frequently in typical myxedema and hypothyroidism, and is the manifestation of functional sluggishness resulting from a lowered basal metabolic rate. Pulse pressure is usually small, resulting from a lowered systolic pressure and is indicative of diminished volume blood outflow.

To summarize the physiology of bradycardia; several factors are involved: (1) The effect of vagus stimulation, and (2) changes affect-

6. Cameron, P. D.: Physiological and Pharmacological Studies on Cardiac Tonicity in Mammals, Johns Hopkins Hosp. Rep. **16**:549 1911.

ing the cardiovascular system independent of innervation influences, (*a*) the secondary effects of a primary bradycardia, and (*b*) primary alterations of the cardiovascular system producing a secondary bradycardia.

CLINICAL OBSERVATIONS

This study comprises 277 patients with bradycardia. The cases were grouped according to rate; ten point pulse differences determined this classification. The upper limit of pulse rate chosen was sixty beats for each minute. The cases were further subdivided into groups: (1) Those with myocardial disease; (*a*) with lesions of the auriculoventricular bundle, and (*b*) without involvement of the bundle; (2) endocardial valvular disease (this group obviously overlaps the previous group but to render it pure, was clearly separated), and (3) vagus augmentation.

Chronic Bradycardia Associated with Myocardial Disease.—This group is exclusive of complete heart block (complete auriculoventricular dissociation). All the patients presented definite evidence of myocardial disease.

Wilson,[7] in an interesting manner, has called attention to the changes affecting the myocardium in later life. He discusses the hardening of tissues by fibrosis as age advances and the effect of this senile degenerative process on the myocardium. The myocardium loses its normal resilience and becomes relatively "rigid."

The physiologic reactions of a myocardium with diminished elasticity and resilience resulting from sclerotic degeneration are extremely interesting. That the sclerosis often involves all the tissues of the heart and the functional interference of cardiac action by a relatively rigid pericardium is obvious.

Diminished elasticity implies diminished amplitude of contraction favoring under-filling and decreased volume outflow. To favor greater filling of the heart, rate is slowed, thereby increasing diastole. If this train of events progresses without increasing contraction amplitude, volume outflow becomes reduced to the point where the syndrome of cerebral anemia occurs. This reaction explains those cases presenting the Adams-Stokes syndrome unassociated with lesions of the auriculoventricular bundle and in which vagus augmentation is not present as determined by atropin response. I have had the opportunity of studying four such cases. Neuhof[8] has called attention to the presence of bradycardia in cardiosclerosis, the prototype of this condition.

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7. Wilson, T. S.: Early Diagnosis of Heart Failure and Other Essays on the Heart and Circulation. New York, Wm. Wood & Co., 1915, pp. 70-142.

8. Neuhof, S.: Clinical Cardiology, New York, Macmillan Co., 1917, p. 99.

The relationship of vagus augmentation to bradycardia occurring with myocardial disease must always be borne in mind, especially in young patients.

The myocardial disease group, exclusive of complete heart block, comprised 152 patients. One patient, a man, 49 years old, presented subjective and objective findings leading to the diagnosis of cardiosclerosis. His average pulse rate was less than 40 each minute and at the time of his initial electrocardiographic examination it was 38. There was normal sequential auriculoventricular rhythm with no evidence of auriculoventricular dissociation at any time during the examination period. He gave no symptoms referable to cerebral anemia. Systolic blood pressure was 128 mm.; diastolic pressure was 64 mm.; pulse pressure, 64 mm.

TABLE 1.—ETIOLOGY OF MYOCARDIAL DISEASE

Rate from 40 to 50

Decade	Cases	Males	Females	Chronic Myocarditis	Syphilis	Hypertension With and Without Clinical Nephritis	Anemia	Cardiosclerosis	Coronary Sclerosis
21–30............	1	1	0	1	1	0	0	0	0
31–40............	4	2	2	3	0	1	0	0	0
41–50............	3	1	2	2	0	1	0	0	0
51–60............	8	8	0	0	0	4	1	2	1
61–70............	5	3	2	1	0	3	0	1	0
71–80............	1	1	0	1	0	0	0	0	0
Total.........	22	16	6	8	1	9	1	3	1
Percentage....	....	72.7	27.3	36.3	4.5	40.9	4.5	13.6	4.5

Syphilis included with chronic myocarditis.

Rate from 40 *to* 50.—Twenty-two patients comprised this group. The apparent etiologic basis of myocardial involvement is noted in Table 1. Chronic myocarditis (36.3 per cent.) and myocardial degeneration accompanying the hypertension group (40.9 per cent.) occurred with greatest frequency. One patient had syphilitic myocarditis. The Adams-Stokes syndrome was not present in this group.

Table 2 summarizes the electrocardiographic findings. The infrequency of auricular fibrillation (4.5 per cent.) is interesting and due probably to the fact that as a group these patients have diminished myocardial irritability. There was no instance of arborization block. Three electrocardiograms revealed nodal rhythm presenting the likelihood of superimposed vagus action.

One-third of the patients had T-wave negativity in their electrocardiograms which are detailed in Table 2. In a recent publication [9] I called attention to the significance of T-wave negativity occurring in isolated and combined derivations of the electrocardiogram and to changes in contraction preponderance resulting from functional or organic myocardial fatigue as being responsible for the negativity. In this connection I wish to consider T-wave negativity as it occurs in the succeeding groups. In the total myocardial group, T-wave negativity occurred in 30 per cent. of the electrocardiograms; in the endocardial valvular group it occurred in 14.2 per cent. and in the vagus group in only 7.4 per cent. This tapering occurrence as the normal myocardium is reached further supports my previous observations on T-wave negativity.

TABLE 2.—MYOCARDIAL DISEASE: ELECTROCARDIOGRAPHIC FINDINGS

Rate from 40 to 50

Decade	Cases	Sinus Bradycardia	Sinus Arrhythmia	Premature Contraction	Auricular Fibrillation	Nodal Rhythm	Arborization Block	Aberrant Q R S in Derivation III	T-Wave Negativity			Ventricular Preponderance		
									Derivation I	Combined Derivations II and III	Derivation III	Left	Right	None
21–30	1	0	1	0	0	0	0	0	0	0	1	1	0	0
31–40	4	1	1	2	1	0	0	0	0	0	0	3	1	0
41–50	3	3	0	0	0	0	0	0	1	0	0	2	1	0
51–60	8	5	0	2	0	1	0	2	0	1	3	3	1	4
61–70	5	2	1	2	0	1	0	0	0	0	0	0	0	5
71–80	1	0	0	1	0	1	0	0	1	0	0	1	0	0
Total	22	11	3	7	1	3	0	2	2	1	4	10	3	9

Preponderance of the left ventricle occurred most frequently (45.4 per cent.); no unbalance occurred next in order of frequency (40.9 per cent.), and preponderance of the right ventricle occurred in only 13.6 per cent. of the tracings. The blood pressure studies are charted in Table 3. Two groups were compiled, the one including all cases and the other excluding those cases with frank hypertension. The increased pulse pressure is evident in both groups, greater obviously in the complete group, but in both instances exceeding the average normal of 50 mm. (67 mm. and 57 mm., respectively). It is at once apparent that the increased pulse pressure occurs through eleva-

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9. Willius, F. A.: Clinical Observations on Negativity of the Final Ventricular Wave T of the Human Electrocardiogram, in press.

tion of the systolic pressure. This group is small and, therefore, averages are open to criticism, yet they are borne out by the larger subsequent groups.

Rate from 50 *to* 60.—There were 129 patients in this group. Table 4 summarizes the apparent etiologic conditions. Chronic myocarditis (47.3 per cent.) and myocardial degeneration associated with the hypertension group (29.4 per cent.) were present with greatest frequency. Six patients had syphilitic myocarditis. Four patients had typical Adams-Stokes seizures in spite of the fact that the auriculoventricular bundle was not obstructed.

TABLE 3.—Myocardial Disease: Blood Pressure Studies

Rate from 40 to 50

	Complete Group					Exclusive of Hypertension				
Decade	Cases	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure	Pulse	Cases	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure	Pulse
21–30.......	1	144	90	54	50	1	144	90	54	50
31–40.......	4	135	80	55	56	2	99	63	36	48
41–50.......	3	169	79	50	48	2	143	73	70	47
51–60.......	8	142	84	58	45	6	136	81	54	46
61–70.......	5	196	87	109	45	1	160	75	85	47
71–80.......	1	122	70	52	46	1	122	70	52	46
Average..	22	156	80	67	48	13	133	77	57	47

TABLE 4.—Myocardial Disease

Rate from 50 to 60

Decade	Cases	Males	Females	Chronic Myocarditis	Syphilis	Hypertension With and Without Clinical Nephritis	Anemia	Cardiosclerosis	Coronary Sclerosis
21–30............	3	2	1	2	0	1	0	0	0
31–40............	16	14	z	14	1	2	0	0	0
41–50............	28	21	7	17	4	7	1	2	1
51–60............	38	33	5	14	0	10	2	4	8
61–70............	38	35	3	12	1	16	1	3	6
71–80............	6	5	1	2	0	2	0	2	0
Total.........	129	110	19	61	6	38	4	11	15
Percentage....	....	85.2	14.7	47.3	4.6	29.4	3.1	8.5	11.6

The electrocardiographic findings in this group are recorded in Table 5. Auricular fibrillation occurred in only a few cases (3.1 per cent.). Twenty-one jatients (16.2 per cent.) had sinus arrhythmia indicative, possibly, of a superimposed vagus action. Arborization block (7.7 per cent.) and aberrant Q R S complexes in isolated derivations of the electrocardiogram (13.9 per cent.) were present in this

group, although not as outstanding occurrences. T-wave negativity was recorded in 30 per cent. of the electrocardiograms. Dominance of preponderance of the left ventricle (.62.0 per cent.) was also present in this group. Right preponderance occurred in only 8.5 per cent. of the tracings and no unbalance was present in 29.4 per cent. Increased work for the left ventricle is the usual order in chronic bradycardia and agrees with the frequency of preponderance of this chamber as revealed by the electrocardiogram.

TABLE 5.—MYOCARDIAL DISEASE: ELECTROCARDIOGRAPHIC FINDINGS
Rate from 50 to 60

Decade	Cases	Sinus Bradycardia	Sinus Arrhythmia	Premature Contractions	Auricular Fibrillation	Arborization Block	Aberrant Q R'S in Isolated Derivation				T-Wave Negativity					Ventricular Preponderance			
							Derivation I	Derivation II	Combined Derivations I and III	Derivation III	Derivation I	Combined Derivations I and II	Combined Derivations II and III	Combined Derivations I, II and III	Derivation III	Prolonged A-V Conduction	Left	Right	None
21–30	3	1	1	1	0	1	0	0	0	0	0	0	0	0	1	0	1	1	1
31–40	16	7	8	1	0	0	0	0	0	0	2	1	0	0	3	1	8	2	6
41–50	28	19	4	5	0	1	0	1	1	3	0	0	0	0	5	0	18	2	8
51–60	38	29	2	5	2	2	0	1	0	2	3	1	2	1	6	1	28	1	9
61–70	38	28	5	6	1	1	1	3	0	0	5	0	3	1	7	3	20	4	14
71–80	6	2	1	3	1	1	0	0	0	0	0	0	0	0	0	0	5	1	0
Total	129	86	21	21	4	10	1	5	3	9	9	1	5	2	22	5	80	11	38

TABLE 6.—MYOCARDIAL DISEASE: BLOOD PRESSURE STUDIES
Rate from 50 to 60

Decade	Complete Group					Exclusive of Hypertension				
	Cases	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure	Pulse	Cases	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure	Pulse
21–30.......	3	131	78	53	52	3	131	78	53	52
31–40.......	16	129	85	44	52	16	129	85	44	52
41–50.......	28	132	82	50	56	24	125	78	47	56
51–60.......	38	148	86	62	56	28	129	78	51	55
61–70.......	38	157	88	69	56	25	140	79	61	56
71–80.......	4	165	86	79	56	3	152	83	69	55
Average..	127*	145	85	60	55	99	131	79	52	55

* Two cases without blood pressure readings.

Table 6 presents the blood pressure readings. An increased pulse pressure is again noted, most marked in the complete group (60 mm.) but not much altered when the frank hypertension readings are excluded (52 mm.). The greater pulse pressure has probably the most accurate value as some of the hypertension readings were

undoubtedly associated with physiologic cardiovascular reactions, especially in those cases in which there were relatively high systolic and normal or slightly elevated diastolic pressures.

The theme of increased pulse pressure is maintained throughout chronic bradycardia.

<div align="center">

COMPLETE HEART BLOCK (COMPLETE AURICULOVENTRICULAR DISSOCIATION)

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I have observed twenty-two patients with complete heart block. The bradycardia associated with this disorder is due to failure of the auricular impulse to pass along the auriculoventricular bundle. Thus the ventricle is not excited to contraction by the impulses arising in the sino-atrial node but assumes an independent rhythm which is slow and often incoordinate. Permanent complete heart block is associated with disease of the auriculoventricular bundle obstructing impulse conduction, although cases in the literature are described in which no lesion was demonstrable.[10]   Cases of transient complete heart block have been reported [11] and our records reveal two such cases.

The apparent etiologic conditions are tabulated in Table 7. Chronic myocarditis occurred in half the cases and chronic endocardial valvular disease and myocardial degeneration associated with the hypertension group in 22.7 per cent., respectively. One case of cardiosclerosis is recorded. Syphilis was not demonstrated in a single instance. Five patients were still free from Adams-Stokes seizures although the heart block was complete.

The blood pressure studies in this group are very interesting (Table 8). The average pulse pressure is large (97 mm.), a marked exaggeration of those in the preceding groups.

Generally, a high systolic pressure indicates strength of cardiac contraction plus adequate filling and emptying, provided the peripheral

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10. Hume, W. E.: A Case of Heart-block in which there was no Pathological Lesion of the Connecting Muscular System. Heart, **5:**149, 1913.

Krumbhaar, E. B.: Adams-Stokes' Syndrome, with Complete Heart-block, without Destruction of the Bundle of His, Arch. Int. Med., **5:**583, (May) 1910.

Pepper, W. and Austin, J. H.: Adams-Stokes' Syndrome, with Complete Heart-block and practically normal bundle of His, Am. J. M. Sc., **143:**716, 1912.

11. Cohn, A. E.: A Case of Transient Complete Auriculo-ventricular Dissociation, Showing Constantly varying Ventricular Complexes, Heart, **5:**5, 1913.

Cohn, A. E. and Lewis, T.: Report of a Case of Transient Attacks of Heart Block, Including a Post-mortem Examination, Heart, **2:**241, 1910.

Heard, J. D. and Colwell, A. H.: A Study of a Case of Intermittent Complete Dissociation of Auricles and Ventricles Presenting Unusual Features. Arch. Int. Med., 18:758 (Nov.) 1916.

Wilson, F. N. and Robinson, G. C.: Heart-block. II. Transient Complete Heart-Block with Numerous Stokes-Adams Attacks, Arch. Int. Med. **21:**181 (Feb.) 1918.

resistance remains constant, influenced, of course, as previously emphasized, by rate. The average systolic pressure was 12 mm. The average diastolic pressure was normal (75 mm.). This, again, illustrates that the increased pulse pressure occurs by elevation of systolic pressure.

TABLE 7.—Complete Heart Block

Decade	Cases	Males	Females	Endo-cardial Valvu-lar Disease	Syphilis	Chronic Myocar-ditis	Hyper-tension With and Without Clinical Ne-phritis	Cardio-sclerosis	Coro-nary Sclerosis
21–30............	1	0	1	0	0	1	0	0	0
31–40............	3	2	1	1	0	2	0	0	0
41–50............	5	3	2	2	0	3	0	0	0
51–60............	2	2	0	1	0	0	1	0	0
61–70............	11	7	4	1	0	5	4	1	0
Total........	22	14	8	5	0	11	5	1	0
Percentage....	....	63.6	36.4	22.7	.....	50.0	22.7	4.5	

TABLE 8.—Complete Heart Block. Blood Pressure Studies

Decade	Cases	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pres-sure	Ven-tricular Rate	Auricular Rate
21–30................	1	158	78	80	48	92
31–40................	3	133	73	60	39	74
41–50................	5	131	75	56	35	74
51–60................	2	185	62	123	36	80
61–70................	11	201	78	123	37	75
Average..........	22	172	75	97	37	76

Musser [12] reported two cases of high systolic pressures in complete heart block, and collected eighteen others from the literature. He also emphasizes increased blood outflow as follows: "This high pressure is dependent more on increased blood mass discharged by the left ventricle than on the associated cardiac hypertrophy and peripheral sclerosis." In our series, eight patients had systolic readings of 200 mm. and over.

That the large pulse pressure is indicative of increased volume outflow of blood is illustrated in the reactions following the administration of thyroxin [13] (thyroid active principle). In a previous publication [14] we reported the use of thyroxin (termed alpha-iodin at

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12. Musser, J. H., Jr.: Heart Block Associated with High Blood Pressure. Arch. Int. Med. **20**:127 (July) 1917.

13. Kendall, E. C.: The Thyroid Hormone. Collected Papers of the Mayo Clinic, Philadelphia, W. B. Saunders Company, **9**:309, 1917.

14. Blackford, J. M., and Willius, F. A.: Chronic Heart Block, Am. J. M. Sc. **154**:585, 1917.

that time) in complete heart block, but no definite conclusions were reached as to the cardiovascular reactions involved. In 1915, Dr. H. S. Plummer suggested the use of thyroxin in complete heart block attended by Adams-Stokes seizures. In Dr. Plummer's observations of a great number of patients suffering with hyperthyroidism he found that the heart in hyperthyroidism delivers an increased output of blood each beat. The first patient subjected. to thyroxin treatment was symptomatically relieved within two weeks, and remained free from the distressing manifestations of cerebral anemia almost three years, but ultimately died of myocardial disintegration.

Interesting changes in this patient's blood pressure readings were observed. On admission to the Clinic he was having from ten to fifteen Adams-Stokes seizures daily. At this time the systolic pressure was 112 mm., diastolic pressure 60 mm., and pulse pressure 52 mm. Subsequent blood·pressure readings during the remaining years of his life showed increased pulse pressure readings due to elevation of systolic pressure. The readings were: systolic pressure, 142 mm., diastolic pressure, 64 mm., pulse pressure, 78 mm.; systolic pressure, 144 mm., diastolic pressure, 78 mm., pulse pressure, 66 mm.; and systolic pressure, 148 mm., diastolic pressure, 76 mm., pulse pressure, 72 mm. These records were taken during practically continuous thyroxin administration over a period of nearly three years. There was no appreciable change in ventricular rate, although the auricular rate accelerated slightly. The relief from the symptoms of cerebral anemia was, therefore, not due to ventricular rate acceleration but to increased volume outflow of blood. Subsequent cases have confirmed the findings in this case. Mackenzie's [15] observations have shown that ventricular standstill for ten seconds produces unconsciousness and for twenty seconds general convulsions of the body. It is obvious that marked diminution of blood outflow of the left ventricle, even without ventricular standstill, may produce cerebral anemia. The relief from thyroxin seems to bear this out. Thyroxin action in effecting increased blood outflow is two-fold: (1) by increasing basal metabolic rate, and (2) by increasing myocardial irritability.

CHRONIC BRADYCARDIA ASSOCIATED WITH CHRONIC ENDOCARDIAL VALVULAR DISEASE

This group is exclusive of complete heart block. It obviously overlaps the myocardial group but has been classified separately to maintain that group clearly. Two factors enter into the chronic bradycardia of this group: (1) myocardial changes (previously discussed), and (2) vagus augmentation.

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15. Mackenzie, Sir J.: Principles of Diagnosis and Treatment in Heart Affections. London, Frowde, 1916, p. 64.

Rate from 40 *to* 50.—There were only eight patients in this group. Six had mitral regurgitation, one mitral stenosis, and another a double mitral lesion. All patients had mild "decompensation." There was nothing outstanding in the electrocardiographic findings, which are summarized in Table 9. Preponderance of the right ventricle occurred in 62.5 per cent. of the cases and would be expected with the high incidence of mitral disease. There was no instance of left preponderance.

Table 10 summarizes the blood pressure readings. The pulse pressure is increased 57 mm. This again occurs through elevation of the systolic pressure.

TABLE 9.—ENDOCARDIAL VALVULAR DISEASE. ELECTROCARDIOGRAPHIC FINDINGS
Rate from 40 to 50

Decade	Cases	Males	Females	Sinus Bradycardia	Sinus Arrhythmia	Premature Contractions	Auricular Fibrillation	Nodal Rhythm	Arborization Block	Aberrant QRS in Derivation I	T-wave Negativity	Ventricular Preponderance		
												Left	Right	None
21–30	1	0	1	0	1	1	0	0	0	0	0	0	1	0
31–40	3	2	1	2	0	1	0	1	0	0	0	0	2	1
41–50	3	2	1	1	2	1	0	0	0	1	0	0	2	1
71–80	1	1	0	0	0	0	1	0	0	0	0	0	0	1
Total	8	5	3	3	3	3	1	1	0	1	0	0	5	3

TABLE 10.—ENDOCARDIAL VALVULAR DISEASE. BLOOD PRESSURE STUDIES
Rate from 40 to 50

Decade	Cases	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure	Pulse
21–30	1	114	90	24	46
31–40	3	141	77	64	47
41–50	3	135	79	56	46
71–80	1	152	80	72	46
Average	8	137	80	57	46

Rate from 50 *to* 60.—Twenty-seven patients were recorded in this group. There were eleven with mitral regurgitation, two with mitral stenosis, four with double mitral lesions, eight with aortic regurgitation, one with double aortic lesion, and one with aortitis and aortic regurgitation. Syphilis was demonstrated in one patient. The electrocardiographic findings are found in Table 11. Preponderance of the left ventricle occurred most frequently (40.7 per cent.). The blood pressure readings are recorded in Table 12. The average pulse pressure is again increased—67 mm. If the blood pressure readings of the

patients having aortic regurgitation are eliminated, the modified average pulse pressure is found to be 58 mm., still greater than normal and due to elevation of the systolic pressure. This theme is reiterated throughout the whole series.

TABLE 11.—ENDOCARDIAL VALVULAR DISEASE. ELECTROCARDIOGRAPHIC FINDINGS
Rate from 50 to 60

Decade	Cases	Males	Females	Sinus Bradycardia	Sinus Arrhythmia	Premature Contractions	Auricular Fibrillation	Nodal Rhythm	Arborization Block	Aberrant Q R S in Derivation I	Aberrant Q R S in Derivation III	Derivation I	Derivation III	Combined Derivations II and III	Combined Derivations I, II and III	Left	Right	None
												T-wave Negativity				Ventricular Preponderance		
11–20..............	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0
21–30..............	6	5	1	2	4	1	0	0	1	0	0	0	0	1	1	0	2	3	1
31–40..............	10	8	2	5	5	0	0	0	0	0	0	0	0	0	0	5	1	4
41–50..............	5	3	2	3	1	0	1	0	1	1	0	1	0	0	0	1	0	4
51–60..............	4	3	1	3	0	0	0	1	0	0	1	0	0	0	1	2	0	2
61–70..............	1	1	0	1	0	0	0	0	0	0	0	0	1	0	1	0	0
Total..........	27	21	6	15	10	1	2	0	2	1	1	1	2	1	1	11	5	11

TABLE 12.—ENDOCARDIAL VALVULAR DISEASE. BLOOD PRESSURE STUDIES
Rate from 50 to 60

Decade	Complete Group					Exclusive of Aortic Regurgitation				
	Cases	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure	Pulse	Cases	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure	Pulse
11–20.......	1	138	64	74	56	1	138	64	74	56
21–30.......	6	145	78	67	58	5	142	86	56	58
31–40.......	10	131	67	64	57	8	125	71	54	57
41–50.......	5	129	65	64	54	1	126	78	48	56
51–60.......	3	154	79	75	57	2	136	68	68	55
61–70.......	1	140	68	72	53	0	0	0	0	0
Total....	26*	137	70	67	56	17	133	75	58	56

* One case without blood pressure readings.

In aortic regurgitation the left ventricle contains more blood than normal, due to the regurgitation of blood backward from the arterial circulation, and thus it is able to contract with its maximal strength on a large volume of blood, giving rise to a relatively increased systolic pressure. The diastolic pressure is usually lowered, and the high pulse pressure results from the large swing affecting the arterial circulation due to the direct blood regurgitation back into the heart. The associated hypertrophy of the left ventricle aids in elevating systolic pressure. The large pulse pressure of aortic regurgitation thus differs from that of chronic bradycardia.

BRADYCARDIA OF VAGUS ORGIN

The effect of vagus augmentation on the cardiac mechanism varies greatly. The most frequent effect is transient slowing of the heart. Patients are encountered running slow heart rates and who may conveniently be grouped under the mysterious term of vagotonia. They are apparently healthy persons with neurotic tendencies, running slow heart rates which accelerate with the administration of atropin. In this group no evidence of organic heart disease was found and no subjective. cardiac complaints, except in a few patients who were conscious of an extrasystolic arrhythmia.

TABLE 13.—Vagus Group. Electrocardiographic Findings

Rate from 40 to 50

Decade	Cases	Males	Females	Sinus Bradycardia	Sinus Arrhythmia	Premature Contractions	Auricular Fibrillation	Nodal Rhythm	Arborization Block	Aberrant Q R S in Isolated Derivations	T-wave Negativity in Derivation III	Ventricular Preponderance		
												Left	Right	None
21–30	5	5	0	2	3	0	0	0	0	0	1	3	0	2
31–40	3	3	0	0	3	0	0	0	0	0	0	0	2	1
41–50	4	3	1	4	0	0	0	0	0	0	1	3	0	1
Total	12	11	1	6	6	0	0	0	0	0	·2	6	2	4

TABLE 14.—Vagus Group. Blood Pressure Studies

Rate from 40 to 50

Decade	Cases	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure	Pulse
21-30................	5	113	70	43	46
31-40................	3	109	73	36	45
41-50................	3	116	77	39	46
Average................	11*	113	73	40	46

* One case without blood pressure readings.

Rate from 40 *to* 50.—There were twelve patients in this group. The electrocardiographic findings are found in Table 13. The blood pressure findings are interesting and contrast sharply those of the preceding groups (Table 14). The average pulse pressure is found to be 40 mm., about 10 mm. less than the average normal. This diminution is effected by a drop in the systolic pressure. It must be emphasized here that the bradycardia of vagus origin is not permanent and hence no permanent alterations in cardiovascular balance occur.

Rate from 50 *to* 60.—This group comprises fifty patients. The electrocardiographic findings are recorded in Table 15 and the blood pressure readings in Table 16. The average pulse pressure is 45 mm., and as in the foregoing group, slightly diminished rather than increased.

<p style="text-align:center">TRANSIENT VAGUS AUGMENTATION</p>

Sino-Atrial Heart Block.—Sino-atrial heart block or transient cardiac standstill is rarely observed and is usually ascribed to vagus stimulation.[16] It, however, has been noted during the administration of digitalis,[17] salicylic acid,[18] aconitin [19] and morphin.[20]

The failure of the auricle to contract may result from (1) failure or weakness of impulse genesis, (2) muscle weakness, or (3) blocking of the impulse between the sino-atrial node and the auricle.

Our series contributes six cases of sino-atrial heart block to the literature and these cases are summarized in Table 17. The patients ranged from 12 to 61 years of age. In only one instance was there evidence of organic heart disease, and that in the oldest patient who presented the clinical findings of a frank myocarditis. In addition to the sino-atrial block, his electrocardiograms revealed delayed auriculoventricular conduction and transient complete heart block. The other cases could be ascribed only to vagus augmentation.

The average pulse rate in this series was 57 each minute. The average systolic pressure 141 mm., diastolic pressure 89, and pulse pressure, 52 mm.

16. Brown, N. W.: Sino-Atrial Heart Block in a Child, with Observations on Effects of Atropin and Vagus Stimulation, Arch. Int. Med. **24**:458 (Oct.) 1919.

Eyster, J. A. E. and Evans, J. S.: Sino-auricular Heart Block, with Report of a Case in Man, Arch. Int. Med., **16**:832 (Dec.) 1915.

Eyster, J. A. E., and Meek, W. J.: Experiments on the Origin and Conduction of the Cardiac Impulse. VII. Sinoventricular and Sinoauricular Heart-Block. Arch. Int. Med., **19**:117 (Jan.) 1917.

Levine, S. A.: Observations on Sino-auricular Heart-block, Arch. Int. Med., **17**:153 (Jan.) 1916.

17. Hewlett, A. W.: Digitalis Heart Block. J. A. M. A., **48**:47 (Jan. 5) 1907.

Parkinson, J.: Digitalis in Soldiers with Cardiac Symptoms and a Frequent Pulse. Heart, **6**:321, 1915.

White, P. D.: Auricular Standstill: An Unusual Effect of Digitalis on the Heart, with Especial Reference to the Electrocardiogram. Boston M. & S. J., **175**:233, 1916.

18. Sicard, M. H. and Meara, F. S.: A Report of Three Cases Showing Vagus Influence. Am. J. M. Sc., **150**:843, 1915.

19. Cushny, A. R.: The Irregularities of the Mammalian Heart Observed Under Aconitine and on Electrical Stimulation, Heart, **1**:1, 1909.

20. Cohn, A. E.: The Effect of Morphin on the Mechanism of the Dog's Heart After Removal of One Vagus Nerve, Jour. Exper. M., **18**:715, 1913.

Eyster, J. A. E. and Meek, W. J.: Experiments on the Origin and Propagation of the Impulse in the Heart, Heart, **5**:137, 1913.

TABLE 15.—Vagus Group. Electrocardiographic Findings
Rate from 50 to 60

Decade	Cases	Males	Females	Sinus Bradycardia	Sinus Arrhythmia	Premature Contractions	Auricular Fibrillation	Nodal Rhythm	Arborization Block	Aberrant Q R S in Isolated Derivations	T-wave Negativity in Derivation III	Ventricular Preponderance		
												Left	Right	None
11–20	5	4	1	1	4	0	0	0	0	0	0	2	1	2
21–30	14	11	3	6	6	3	0	0	0	0	3	1	6	7
31–40	15	13	2	11	4	1	0	0	0	0	0	1	1	13
41–50	13	13	0	10	3	0	0	0	0	0	0	1	3	9
51–60	3	3	0	2	1	0	0	0	0	0	0	0	1	2
Total	50	44	6	30	18·	4	0	0	0	0	3	5	12	33

TABLE 16.—Vagus Group. Blood Pressure Studies
Rate from 50 to 60

Decade	Cases	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure	Pulse
11–20	5	132	70	62	53
21–30	13	118	76	42	57
31–40	14	124	78	46	56
41–50	12	117	76	41	56
51–60	3	127	76	51	57
Average	47*	121	76	45	55

* Three cases without blood pressure readings.

TABLE 17.—Sino-Atrial Heart Block
Rate from 50 to 60

Cases	Males	Females	Age, Years	Premature Contractions	Aberrant Q R S in Derivation III	Aberrant Q R S in Combined Derivations II and III	Prolonged Pulse Rate Interval	Complete Heart Block	T-wave Negativity in Derivation III	Ventricular Preponderance		
										Left	Right	None
1	1	0	12	0	1	0	0	0	0	0	0	1
1	0	1	33	0	0	1	0	0	1	0	0	1
1	0	1	39	0	1	0	0	0	0	0	0	1
1	1	0	46	1	0	0	0	0	0	1	0	0
1	0	1	57	0	0	0	0	0	0	1	0	0
1	1	0	61	0	0	0	1	1	0	0	0	1
6	3	3	..	1	2	1	1	1	1	2	0	4

Ventricular Escape.—Ventricular escape, a relatively rare disorder of the cardiac mechanism, is at times due to transient vagus augmentation. In this disorder, the ventricle occasionally escapes from the influence of the sino-atrial node through independent automatism of the atrioventricular node. Two types of ventricular escape occur:[21] (1) resulting from depression of the sino-atrial node so that the atrioventricular node asserts itself by virtue of its inherent automatism, and (2) resulting from increased irritability of the atrioventricular node. In the type resulting from vagus augmentation, the sinus rate is slow. One case of ventricular escape has been observed, apparently of vagus origin.

<div align="center">COMMENT</div>

Chronic bradycardia is discussed, including physiologic reactions involved, and a consideration of various types of bradycardia and associated conditions.

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21. White, P. D.: Ventricular Escape with Observations on Cases Showing a Ventricular Rate Greater than that of the Auricles, Arch. Int. Med., **18**:244, 1916.

THE USE OF A HIGH FAT DIET IN THE TREATMENT OF DIABETES MELLITUS *

FIRST PAPER

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The treatment of diabetes mellitus has been very greatly improved in the recent past, owing to the work of Allen [1] and his colleagues. It has been shown by him that the urine of the severest diabetics can be made sugar free by sufficiently prolonged starvation and will remain sugar free if the total energy intake is kept sufficiently small.

It has been the general custom to make up the diet largely of protein, because of the undoubted desirability of omitting carbohydrates, and because of the almost universal fear of precipitating a dangerous acidosis by allowing more than a minimum of fat. This high protein, low fat, low carbohydrate diet, given in quantities sufficient to maintain metabolic needs, is accompanied by a glycosuria in the severe diabetics. In order to prevent glycosuria, it is necessary to restrict the total energy intake so much that inanition results. In other words, this leaves the physician the choice of one of two procedures. On the one hand, he may keep the patient sugar free, but in so doing, because of the low energy intake, he renders him unfit for the ordinary activities of life. On the other hand, if he aims to avoid this incapacity for his patient, he must expect him to continue to suffer from the effects of hypergylcemia.

It is evident that the two horns of the dilemma can be avoided if the diabetic can safely be given enough calories to maintain metabolic equilibrium, without producing hyperglycemia or acidosis. Since carbohydrate cannot be used, and since protein is, as just pointed out, unsatisfactory, we have dared to ignore the belief concerning the danger of fat in the diet of diabetics, and have investigated in the clinic the effect of a diet whose energy comes largely from fat, to

1. Allen, F. M.: Tr. A. Am. Phys. **32**:138, 1917; Am. J. M. Sc. **153**:313, 1917.

which is added sufficient protein to maintain nitrogen equilibrium and the minimal carbohydrate necessitated in making up a diet that a human being can eat over a long period of time.

For the purpose of studying this question, we have adopted a routine procedure. When a patient enters the clinic, he is placed on a diet containing from 900 to 1,000 calories, of which about 90 gm. is fat, 10 gm. is protein and 14 gm. is carbohydrate. After the patient has been sugar free for one or two weeks, his diet is increased to about 1,400 calories, of which 140 gm. is fat, 28 gm. is protein and from 15 to 20 gm. is carbohydrate. In the cases of small individuals this diet is sufficient for prolonged use, and some of them are discharged with instructions to continue it. For larger persons, after another period of trial, a second increase is made, reaching 1,800 calories, containing 170 gm. of fat, from 30 to 40 gm. of protein, and from 25 to 30 gm. carbohydrate. Further additions up to 2,500 calories may be made to suit individual cases.

In order to prove that our procedure is an improvement over the usual method, we must show, (1) that glycosuria is avoided in severe diabetics; (2), that this diet does not precipitate acidosis; (3), that nitrogen equilibrium is maintained, and (4), that the patients are able to lead at least a moderately active, comfortable life.

We have thus far had the opportunity of studying the effect of our method in the treatment of seventy-three cases of true diabetes mellitus. There has been no selection of cases—every patient entering the service has been placed on this regimen. The majority of these seventy-three cases have been of the severest type. This follows from the fact that the physicians of the state consider the University Hospital the court of last appeal, and send us those patients who do not respond to simple diabetic measures.

In spite of the fact that so many of our cases were of the severe type, we have succeeded in rendering and keeping every patient sugar free up to the time of discharge. The following case is an example of the response of a severe diabetic to our treatment.

REPORT OF CASE

Case 1 (No. 20-426).—A woman, aged 34 years, entered the clinic June 8 with a letter from her family physician in which he stated that he had been unable to render her urine free of sugar, even though he had starved her for nearly a week. She confirmed his story and said that she was so weak that she could hardly walk.

She was immediately placed on our first high fat diet, containing 900 calories. It was not until June 25, that the last trace of sugar disappeared from her urine. The ferric chlorid test became negative June 29. July 1, her diet was increased to 1,400 calories, of which 140 gm. were fat, and July 9 it was again increased to 1,800 calories, of which 170 gm. were fat. During her last week in the hospital, she took a walk after each meal and stated that she had

practically regained her normal strength. At no time after its first disappearance did glycosuria develop. She was discharged July 15 on the diet containing 1,800 calories, of which 170 gm. were fat, 40 gm. protein and 25 gm. were carbohydrate.

In order to show that the usual high protein diet is accompanied by glycosuria in these severe diabetics, we have submitted three of our patients, previously made sugar free by means of our diet containing 90 gm. of fat and 16 gm. of protein, to such a high protein diet. Each one of these individuals became glycosuric as a result of this change to a high protein diet and was again quickly made sugar free by a return to the original diet.
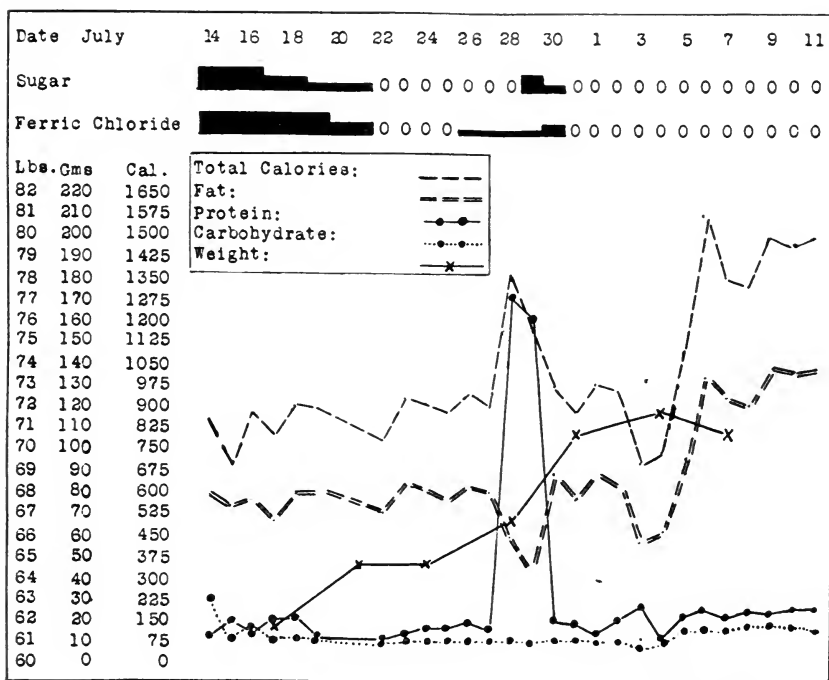

Fig. 1—Case 2 (20-475). Showing (1) disappearance of urinary sugar on high fat diet; (2) its reappearance on high protein diet; (3) its disappearance again on high fat diet and (4) its continued absence with increase of calories by addition of fat.

CASE 2 (No. 20-475).—A woman, aged 33 years, who on a low carbohydrate high protein diet, had lost 40 pounds' weight in a year, entered the clinic July 14, weighing 62 pounds. On a diet of 18 gm. protein, 80 gm. fat and 14 gm. carbohydrate, totaling 900 calories, her urine became sugar free July 21, and remained so during the following week. On each of two days, July 28 and 29, she received 170 gm. protein, 55 gm. fat and 12 gm. carbohydrate, totaling 1,200 calories. July 30 she was returned to her former diet. The urine of July 29 and 30 contained, respectively, 11 and 3 gm. glucose. The urine of July 31 was sugar free. August 5, her diet was increased to 1,400

calories, with 25 gm. protein, 140 gm. fat and 20 gm. carbohydrate. On this diet her urine has remained sugar free. The data are presented graphically in Figure 1.

CASE 3 (No. 20-461).—This patient was brought to the clinic July 2, 1920, on the verge of coma. He was confused, so weak that he could not stand, and showed the classic Kussmaul breathing. As a result of our first high fat diet (containing 90 gm. fat and 900 calories), sugar disappeared from his urine July 13. The acidosis disappeared on the same day. July 20, after having shown no sugar in his urine for a week, he was placed on a diet containing 900 calories, of which about 130 gm. were protein. His total calories were the same as on the high fat diet, and his carbohydrate intake was unchanged. His urine on the fourth and fifth day of this diet contained sugar. Clearly, the return of glycosuria in a patient previously sugar free on our high fat diet was due to the substitution of protein for fat.
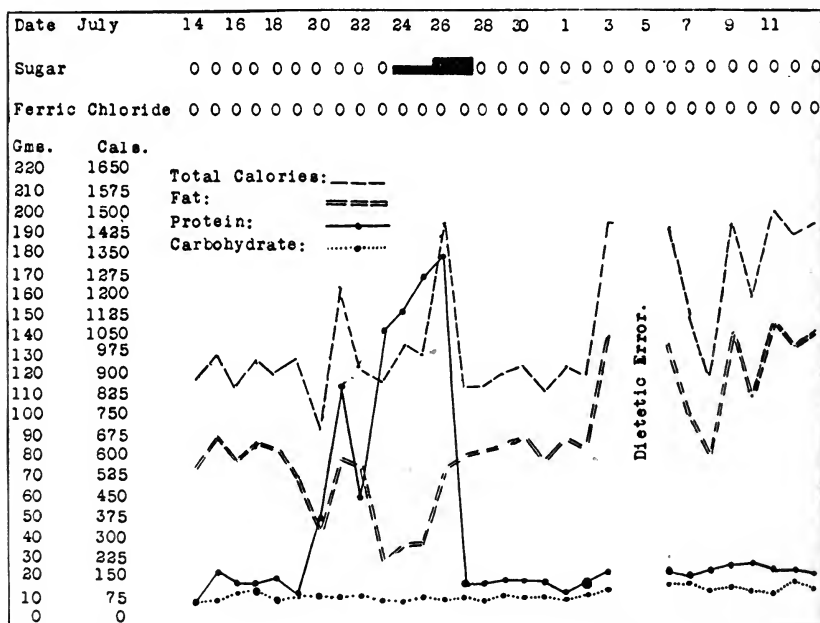
Fig. 2.—Case 3 (20-461). Showing (1) absence of urinary sugar on high fat diet; (2) its reappearance on high protein diet; (3) its disappearance on subsequent high fat diet and (4) its continued absence with increase of calories by addition of fat.

We felt it was highly desirable to feed this patient 1,500 calories in order to avoid inanition, provided, also, that this could be done without producing a return of the diabetic state. Accordingly we gave him the desired number of calories, made up in the usual way, largely of protein. The diet had the following composition: Total calories, 1,483; protein, 181 gm.; fat, 78 gm.; carbohydrate, 14 gm. His urine the next day contained 11.4 gm. sugar. Only one day of this diet was required to convince us that it was unsuitable, and he was returned to the original high fat diet. On the second day of this latter diet, his urine became sugar free, and remained so. August 1, his calories

were increased to 1,500, of which 150 gm. were fat, 30 gm. protein, and 20 gm. carbohydrate. He continued to remain sugar free, made a gain in weight (from 88 to 97 pounds) in two weeks, and was furnished slightly more than 0.66 gm. protein per kilogram of body weight. This diet, then, of 1,500 calories, containing 150 gm. fat, fulfilled our two specifications; first, that he remain sugar free, and second that he suffer no inanition. The data from August 13 to July 11, are presented graphically in Figure 2.

CASE 4 (No. 20-427).—This man had had a severe diabetes which had never been treated systematically before his entrance to the hospital June 9. After four days of our fat diet, he became sugar free. July 26, after he had been sugar free for nine days on a diet of 28 gm. protein, 130 gm. fat, and 20 gm. carbohydrate, totaling 1,400 calories, he was given the same 1,400 calories, of which 185 gm. were protein, 50 gm. were fat and 12 gm. were carbohydrate. The urine of July 29 and 30 contained 6.4 and 7.2 gm. sugar, respectively. July 30 he was returned to the original 900 calories, high fat diet, and the next day his urine was sugar free. His diet was then increased according to our usual procedure, and he was still sugar free when he left the hospital.

All three of these patients demonstrated their inability to tolerate, without glycosuria, a diabetic diet of the ordinary type containing a relatively large amount of protein. Yet they readily and promptly responded to our high fat diet with a disappearance of urinary sugar. Two diets of the same number of calories, one rich in protein and the other rich in fat, produced a glycosuria in the first case and no glycosuria in the second. These experiments, coupled with the fact that we have yet to see a patient who does not become sugar free on our regimen, justify us in believing that patients who would continue to have a glycosuria on the standard high protein diet, containing sufficient calories to prevent inanition, may be· expected to become and remain sugar free on a diet of the same number of calories of which nearly all are in the fat content.

Having in mind the prevailing fear of the use of fat in the diet of diabetics we were very much surprised to find, when fat is used, as we used it in the management of our seventy-three cases, that such fear is entirely ungrounded. In no case did a serious acidosis develop. It is true that four of these seventy-three patients died in the hospital, but none of these deaths was due to our diet. One patient entered the hospital with influenzal pneumonia. Another one was transferred from the surgical clinic suffering from a severe sepsis accompanying suppurative mastoid disease. Both of these patients died within twenty-four hours after their admission to the medical service. The third patient came to the hospital in coma and died ten hours after admission. The fourth patient refused to limit herself to the diet, and went into coma after eating a bag of oranges brought by a relative. None of these fatalities can, by any stretch of the imagination, be attributed to the high fat diet. In no case did the much feared fat produce any untoward symptoms.

Not only was this true, but unexpectedly enough, acidosis, even though marked, existing at entrance, invariably cleared up under our treatment. The following cases are examples of this beneficial effect on the acidosis.

Case 3 (No. 20-461) shows how the high fat diet may be attended by the gradual diminution and final disappearance of acidosis. This patient was brought to the hospital June 30 in a semicomatose condition, with the air hunger typical of extreme acidosis. An idea of the severity of the acidosis may be obtained from noting the fact that 157 gm. of sodium bicarbonate during the seventeen hours after his admission failed to make his urine neutral. July 2, when he had recovered from his stupor sufficiently to be able to eat, he was placed on our routine diet with its 90 gm. of fat daily. July 13, eleven days later, his urine was sugar free, and on the same day the ferric chlorid test on his urine became negative.

Case 2 (No. 20-475) shows well the simultaneous disappearance of sugar and ferric chlorid reaction from the urine of a severe diabetic, as a result of our high fat diet. The data are presented in Table 1.

TABLE 1.—Relation of Diet to Disappearance of Sugar and Acetone Bodies from Urine

Date	Urinary Sugar*	Ferric Chlorid Reaction
July 14 (entrance)	++++	++++
15	15.6	+++
16	22.0	++++
17 (part specimen)	0.0	++++
18	6.9	++++
19	1.0	++++
20	4.7	+++
21	4.1	++++
22	0.0	0
23	0.0	0

* Sugar is expressed in grams per twenty-four hours. Ferric chlorid ++++ means that the typical color reaction was still obtained after the urine had been diluted four times with equal volumes of water.

Case 4 (No. 20-427), a severe diabetic already described above, never showed more than a trace or "one plus" of ferric chlorid reaction in his urine.

Case 5 (No. 19-537).—The patient, a severe diabetic, 21 years old, ran the usual clinical course on our diet. The data are presented in Table 2.

The patient, who is Case 6 in this report, is being treated experimentally in the department of pediatrics, and his case is cited through the courtesy of Dr. D. M. Cowie. Because of the well known fact that diabetes in young children is especially severe and usually rapidly fatal, we consider this case of great value as evidence in support of the view that a high fat diet is not attended by dangerous acidosis.

TABLE 2.—Relation of Diet to Disappearance of Sugar and
Acetone Bodies from Urine

Date, 1919	Urinary Sugar	Ferric Chlorid Test	Blood Sugar	Carbon Dioxid Tension of Alveolar Air
Nov. 23	++++	+	0.30	
24	+++	+		
25	+++	+		
26	++	+		
27	+	+	0.21	
28	++	+		
29	+	+	....	30.0
30	+	+	....	40.6
31	0	+		
Dec. 1	0	0		
2	0	0		
3	0	0	0.176	45.0
4	0	0		
5	0	0		
6	0	0		

Case 6 (No. 4923).—A boy, 7 years old, entered the hospital Oct. 15, 1919, complaining of increasing weakness and great loss of weight. The carbon dioxid tension of the alveolar air was 20 mm. mercury. The therapeutic result as regards glycosuria was not entirely satisfactory because the boy occasionally departed from his diet. The case does, however, show the inocuousness of a long continued high fat diet. The data during a period when the diet was characterized by its high fat content, are presented in Figure 3.

It is not necessary to describe more cases than these because those presented are typical and characteristic of the whole series. Even though we are repeating, we feel it necessary to point out again that none of the patients whom we treated by means of our high fat diet developed a severe acidosis. It is true, on the contrary, that the evidence of acidosis progressively decreased day by day until it had invariably become negligible.

No diet can be considered adequate in the treatment of diabetes unless it will maintain nitrogen balance. Our diet is comparatively low in protein, and is open to the possible criticism that it contains insufficient nitrogen. It has been shown by several observers, and notably by Hindhede,[2] that less than 0.66 gm. protein per kilogram of body weight, in the presence of sufficient calories from other sources, is more than enough to maintain nitrogen balance in healthy ordinarily active human beings. Our diet is constructed with this requirement in mind, and is so arranged that it contains at least 0.66 gm. protein per kilogram of body weight before the patient is discharged from the clinic.

But what is true for the normal man may not hold for the diabetic. It accordingly becomes necessary to determine the actual ratio between the nitrogen intake and nitrogen output of diabetics on our diet. This was done by the usual procedure. The intake was computed from

2. Hindhede: Skand. Arch. Physiol. **30:**97, 1913.

TABLE 3.—CASE 19-444, SHOWING THE NITROGEN METABOLISM OF A DIABETIC BEING FED A HIGH FAT LOW PROTEIN DIET*.

Date	Urine Volume	Glucose Urine	Blood Sugar	Body Weight	Stool Weight	Intake					Output		Nitrogen Balance
						Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Nitrogen Intake	Nitrogen Urine	Nitrogen Stool	
9/ 5	3,200	+++	0.52	95.0	..	16.30	97.40	9.87	1,008				
9/ 6	3,525	+++	....	....	..	16.30	97.40	9.87	1,008				
9/ 8	2,110	+++	0.36	....	..	16.30	97.40	9.87	1,008				
9/10	2,930	+++	0.29	....	..	16.30	97.40	9.87	1,008				
9/12	2,880	+++	0.24	91.0	..	16.30	97.40	9.87	1,008				
9/15	2,700	++	0.20	....	..	16.30	97.40	9.87	1,008				
9/16†	......	....	....	....	..	.....	.....	...	.....				
9/17	?	+++	0.42	....	..	16.30	97.40	9.87	1,008				
9/18	3,000	+++	....	....	..	16.30	97.40	9.87	1,008				
9/21	3,100	+++	0.23	87.0	..	16.30	97.40	9.87	1,008				
9/22	2,900	0	....	....	..	16.30	97.40	9.87	1,008				
9/25	2,600	0	0.15	85.5	..	16.30	97.40	9.87	1,008				
9/30	2,500	0	....	85.5	..	24.87	141.42	9.89	1,458				
10/ 1	2,500	0	....	85.0	..	24.87	141.42	9.89	1,458				
10/ 2	2,250	0	0.16	85.0	..	24.87	141.42	9.89	1,458				
10/ 3	2,750	0	....	84.0	..	24.87	141.42	9.89	1,458				
10/ 4	1,510	0	....	84.5	..	24.87	141.42	9.89	1,458				
10/ 5	2,650	0	....	86.2	..	24.87	141.42	9.89	1,458				
10/ 6	2,085	0	....	86.0	..	24.87	141.42	9.89	1,458				
10/ 7	1,200	0	0.15	86.2	99	24.87	141.42	9.89	1,458	3.019	6.714	0.940	−3.675
10/12	2,585	0	0.13	88.5	..	36.82	192.87	9.87	1,981				
10/13	2,050	0	0.15	88.5	..	36.82	192.87	9.87	1,981				
10/14	2,800	0	....	88.0	..	36.82	192.87	9.87	1,981				
10/15	1,460	0	0.18	88.0	..	36.82	192.87	9.87	1,981				
10/16	2,600	0	....	88.0	..	36.82	192.87	9.87	1,981				
10/17	1,750	0	....	87.0	92	36.82	192.87	9.87	1,981	5.891	5.375	0.929	−0.929
10/22	1,055	0	....	89.5	..	36.82	192.87	9.87	1,981				
10/23	1,115	0	....	90.0	..	36.82	192.87	9.87	1,981				
10/24	1,420	0	0.15	92.5	39	36.82	192.87	9.87	1,981	5.891	4.855	0.913	+0.123
10/26	1,430	0	....	93.5	..	36.82	166.20	9.87	1,682				
10/27	1,535	0	....	94.0	..	36.82	166.20	9.87	1,682				
10/28	1,500	0	....	94.5	..	36.82	166 20	9.87	1,682				
10/29	2,000	0	....	94.5	..	36.82	166.20	9.87	1,682				
10/30	1,708	0	....	94.5	..	36.82	166.20	9.87	1,682				
10/31	2,470	0	0.15	94.2	42	36.82	166.20	9.87	1,682	5.891	2.433	0.421	+3.037
11/ 1	2,030	0	....	94.5	..	36.82	166.20	9.87	1,682				
11/ 2	2,420	0	....	93.0	..	36.82	166.20	9.87	1,682				
11/ 3	1,700	0	....	93.0	..	36.82	166.20	9.87	1,682				
11/ 4	1,850	0	....	92.5	..	28.08	162.80	9.87	1,604				
11/ 5	2,120	0	....	92.5	..	28.08	162.80	9.87	1,604				
11/ 6	1,800	0	....	92.0	..	28.08	162.80	9.87	1,604				
11/ 7	1,920	0	0.15	91.5	35.5	28.08	162.80	9.87	1,604	5.092	2.965	0.455	+1.672
11/11	2,235	0	....	92.5	..	28.08	162.80	9.87	1,604				
11/12	2,365	0	....	92.2	..	28.08	162.80	9.87	1,604				
11/13	2,425	0	....	92.5	..	28.08	162.80	9.87	1,604				
11/14	1,950	0	....	92.0	46	28.08	162.80	9.87	1,604	4.492	1.211	1.150	+2.130

* The studies in the nitrogen metabolism of the diabetics were made by Dr. C. E. Roser, at that time a member of the medical staff of the University Hospital. His heroic labors at the time of the last influenza epidemic unfortunately resulted in his death. We who knew him realize that medicine has lost one of her most promising devotees. All his work was characterized by zeal, intelligence and rugged honesty. We take this opportunity of acknowledging our deep indebtedness to him in this investigation, and of expressing our grief occasioned by his loss.

† The patient left the hospital at this time without permission and during one day ate about 75 gm. protein, 60 gm. fat, 371 gm. carbohydrate, equal to 2,350 calories. Returned next day.

Atwater and Bryant's Food Tables, and the output in the urine and stool was quantitatively determined by the Kjeldahl method. Eight cases were completely studied in this way. We present, in Table 3, the data obtained from one of these, Case 7 (19-444).

It will be seen from this table that 25 gm. of protein daily were not sufficient to establish nitrogen balance in the short time allowed, whereas 28 gm. were more than enough. Theoretically, on the basis of 0.66 gm. protein per kilogram of body weight, this patient requires 26
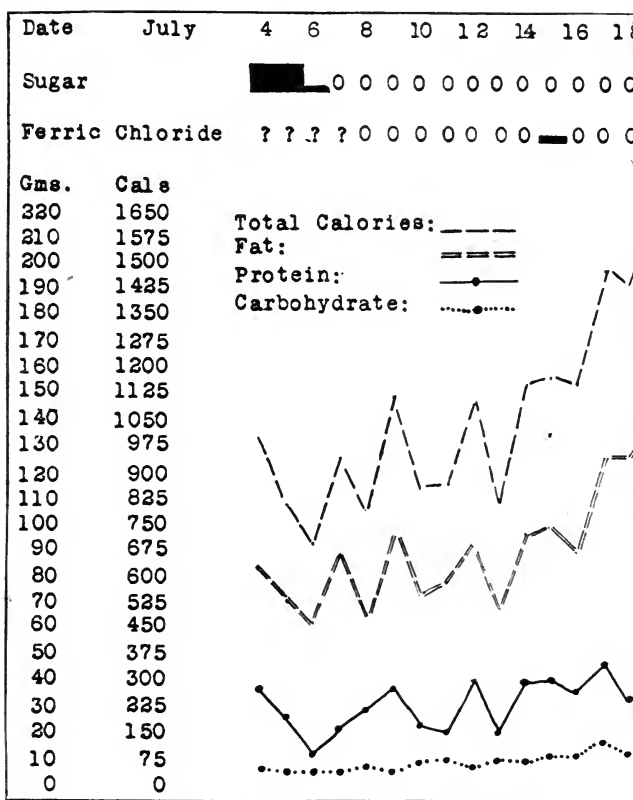
Fig. 3.—Showing absence of acidosis in a child fed a high fat, low protein diet.

gm. protein daily, computed from a weight of eighty-eight pounds. At his discharge weight, he would require 28 gm. of protein daily. But, as already pointed out, it has been shown for normal man that the "two-thirds of a gram per kilo" rule may be expected to supply more than enough nitrogen. This same relationship holds in this diabetic patient, who, when eating 0.66 gm. of protein per kilo of body weight has an excess of more than 2 gm. daily over nitrogen balance.

The other cases studied by this method showed a similar relationship between protein need and body weight, and convinced us that nitrogen balance could be safely maintained by feeding 0.66 gm. of protein per kilogram of body weight in the diabetic as in the normal man. This makes any argument on this score against our high fat, low protein diet, untenable.

A diabetic diet, in order to be satisfactory, must be capable of enabling the patient to lead a moderately active life for an indefinite period. As has already been pointed out, the severe diabetic may be kept sugar free by a sufficient reduction of his total caloric intake, but it is frequently necessary to reduce the total calories so much when protein is used as the chief source of energy that such patients suffer from slow starvation, and are quite incapable of earning a livelihood—indeed many of them may be said to merely exist. From the point of view of the patient, who does not fully appreciate the dangers of continued hyperglycemia, such a situation is a poor exchange for that which he had before treatment. While our experience with the high fat diet has been brief in relation to the chronicity of the disease and we are not in a position to discuss the eventual results of our diet, we are, nevertheless, greatly impressed by the excellent condition of our patients months after leaving the clinic. The strength and capacity for work of some of our younger patients is astonishing to one who has seen many severe diabetics treated by the older methods. We cite a few cases as examples of this point.

CASE 8 (No. 20-19).—A young man, 22 years old, entered the clinic Jan. 16, 1920, weighing 113 pounds. After five weeks of treatment he was discharged on a diet containing 2,000 calories, of which 40 gm. were protein, 25 gm. carbohydrate and the remainder fat.

Since then, he has returned at frequent intervals for examination. On every occasion he has been sugar free, and he has gained 9 pounds in weight. May 7, less than four months after he came to us, he began working in a machine shop, at a stamping machine, which keeps him on his feet constantly. August 20 when last seen by us, he stated that he was feeling entirely well, that he had had no difficulty in doing his work and that he found his diet very pleasant.

CASE 9 (No. 19-286).—A man, aged 40, who had had glycosuria for ten years before coming to us, entered the clinic because he was continuously losing weight and strength, because of increasing numbness of the feet, accompanied by prickling sensations in the legs, and because of serious and increasing impairment of vision. On admission, June 5, 1919, his blood sugar was 0.4 per cent. By June 9, as a result of our diet containing 900 calories, he was sugar free. By June 25 his diet had been increased to 2,500 calories and consisted of 243 gm. fat, 48 gm. protein, and 15 gm. carbohydrate. He was discharged June 30, 1919, with this diet, weighing 129 pounds.

March 30, 1920, nine months later, he returned for examination stating that he had felt entirely well during the interval and that he had had no difficulty in carrying on his work as a traveling salesman. He weighed 124 pounds and his urine was sugar free.

Case 10 (No. 20-420).—A woman, aged 32 years, entered the clinic June 5, 1920, complaining of weakness of more than a year's duration. Her condition had become such that she had not been able to do her housework, and if she walked about she fainted. She was started on our routine high fat diet containing 900 calories and became sugar free in five days. Her diet was increased by the usual steps until it reached from 1,800 to 2,000 calories of which about 170 gm. were fat. She left the hospital June 15, 1920, on this diet. A month later she returned for examination stating that she had gained 3 pounds and that she was doing her housework for the first time since January, 1919. Her urine was sugar free and there was no reaction with ferric chlorid.

SUMMARY

Patients with severe diabetes, as a class, do not remain sugar free on the usual high protein diet unless the total energy intake is kept so low that incapacity from starvation results. The only satisfactory diet is one which will keep the diabetic sugar free, which will prevent the occurrence of serious acidosis, which will maintain nitrogen balance and which will make it possible for him to resume the ordinary activities of life. With these four points in mind, we studied the effect of a high fat, low protein, low carbohydrate diet in the treatment of diabetes. Our experience with this type of diet in the management of seventy-three diabetics has convinced us that it is capable of fulfilling these four specifications.

APPENDIX

Following are examples of high fat, low protein, low carbohydrate diets of varying caloric value.

Diabetic Diet No. 1. Example 1

Dinner	Protein, Gm.	Fat, Gm.	Carbohyd., Gm.	Calories
Chicken, 2 oz.	12.2	1.4	....	61.6
with butter, ⅔ oz.	0.2	17.0	....	153.8
Cabbage, 2 oz.	0.9	0.18	3.18	17.8
with vinegar, salt and pepper.				
Asparagus, 3 oz.	1.53	0.18	2.8	18.9
with butter, ⅓ oz.	0.1	8.5	....	76.9
3 olives, medium size	0.12	4.6	1.94	50.0
Broth	....	.....	....	....
Tea	....	.....	....	....
Supper				
Lettuce, 2 oz.	0.68	0.18	1.64	10.8
with mayonnaise, 1⅓ oz. (oil, 1 oz.)	....	28.35	....	255.1
Tomatoes, 4 oz.	1.02	0.18	3.4	19.2
with butter, 10 gm.	0.1	8.5	....	76.9
Broth	....	.....	....	....
Tea	....	.....	....	....
Breakfast				
Lettuce, 2 oz.	0.68	0.18	1.64	10.8
with ground bacon, 1 oz.	2.98	18.37	....	177.2
Broth	....	.....	....	....
Coffee	....	.....	....	....
Total	20.51	87.62	14.6	929.0

DIABETIC DIET No. 1. EXAMPLE 2

Dinner	Protein, Gm.	Fat, Gm.	Carbohyd., Gm.	Calories
Boiled ham, 1 oz..................	5.72	6.35	....	80.0
Spinach, 3 oz......................	1.77	0.27	2.73	20.4
with vinegar, salt and pepper.				
Asparagus, 3 oz...................	1.29	0.09	2.37	15.3
with butter, 20 gm..............	0.20	17.0	....	153.8
Tea	....	.....	....	....
Broth	....	.....	....	....
Supper				
Cabbage, 2 oz.....................	0.9	0.18	3.18	17.8
with ground bacon, ½ oz.........	1.49	9.18	....	88.6
String beans, 3 oz.................	1.95	0.27	6.3	35.4
with French dressing.				
Oil, 1 oz.........................	....	28.35	....	255.1
Vinegar, ½ oz., salt and pepper.				
Broth	....	.....	....	....
Tea	....	.....	....	....
Breakfast				
Bacon, ⅔ oz......................	2.1	13.96	....	125.0
1 egg	6.03	4.72	....	66.5
Broth	....	.....	....	....
Coffee	....	.....	....	....
Total	21.46	80.37	14.58	858.0

DIABETIC DIET No. 1. EXAMPLE 3

Dinner	Protein, Gm.	Fat, Gm.	Carbohyd., Gm.	Calories
Cottage cheese, 1 oz..............	5.92	0.28	1.21	31.1
Lettuce, 2 oz......................	0.68	0.18	1.62	10.8
with mayonnaise, 1 oz............	....	20.04	....	191.4
Tomatoes, 3 oz....................	1.02	0.18	3.39	19.2
with butter, ⅓ oz................	0.1	8.5	....	76.9
Broth	....	.....	....	....
Tea	....	.....	....	....
Supper				
Cabbage, 1½ oz....................	0.67	0.13	2.38	46.6
with mayonnaise, 1⅓ oz. (oil, 1 oz.)	....	28.35	....	255.1
Spinach, 4 oz.....................	2.36	0.36	3.64	27.2
with butter, ⅓ oz................	0.14	12.4	....	108.9
Broth	....	.....	....	....
Tea	....	.....	....	....
Breakfast				
1 egg	6.03	4.72	....	66.6
with butter, ⅓ oz................	0.1	8.5	....	76.9
Cream, 1½ oz. (18%)..............	1.2	8.4	2.1	88.8
Broth	....	.....	....	....
Coffee	....	.....	....	....
Total	18.22	91.68	14.34	999.5

DIABETIC DIET No. 1. EXAMPLE 4

Dinner	Protein, Gm.	Fat, Gm.	Carbohyd., Gm.	Calories
Steak, 2 oz........................	9.31	8.67	....	115.7
with butter, ⅓ oz................	0.1	8.5	....	76.9
Cabbage, 2 oz......................	0.9	0.18	3.18	17.8
with ground bacon, 1 oz..........	2.98	18.37	....	177.2
Tomatoes, 3 oz....................	1.02	0.18	3.49	19.2
Broth	....	.....	....	....
Supper				
Lettuce, 2 oz......................	0.60	0.18	1.64	10.8
with mayonnaise, 1⅓ oz..........	....	28.35	....	255.2
Asparagus, 3 oz....................	1.53	0.18	....	18.9
with butter, ⅔ oz................	0.2	17.0	....	153.8
Tea	....	.....	....	....
Broth	....	.....	....	....
Breakfast				
Lettuce, 2 oz......................	0.68	0.18	1.64	10.8
with vinegar, salt and pepper.				
½ hard cooked egg...............	3.01	2.36	....	33.3
Broth	....	.....	....	....
Coffee	....	.....	....	....
Total	20.41	84.15	12.75	889.6

DIABETIC DIET No. 1. EXAMPLE 5

Dinner	Protein, Gm.	Fat, Gm.	Carbohyd., Gm.	Calories
Boiled ham, 1½ oz. (medium fat)..	8.41	8.35	....	113.2
Asparagus salad:				
Lettuce, 1 oz.....................	0.34	0.09	0.82	5.4
Asparagus, 3 oz..................	1.53	0.18	2.8	18.9
Mayonnaise, 1⅓ oz. (oil, 1 oz.)...	....	28.35	....	255.2
String beans, 2½ oz................	1.6	0.22	5.2	29.5
with butter, ½ oz................	0.14	12.04	....	108.9
Broth	....	.....	....	....
Tea	....	.....	....	....
Supper				
Tomatoes, 3 oz....................	1.02	0.18	3.39	19.2
Lettuce, 1 oz......................	0.34	0.09	0.82	5.4
with mayonnaise, ⅔ oz. (oil, ½ oz.)	....	14.2	....	127.6
Broth	....	.....	....	....
Tea	....	.....	....	....
Breakfast				
Omelet: 1 egg....................	6.03	4.72	....	66.6
Butter, ⅓ oz.....................	0.1	8.5	....	16.9
Cream, 1 oz. (18%), for coffee.....	0.8	5.6	1.4	59.2
Broth	....	.....	....	....
Total	20.31	83.02	14.43	886.2

DIABETIC DIET No. 2. EXAMPLE 1

Dinner	Protein, Gm.	Fat, Gm.	Carbohyd., Gm.	Calories
Chicken, 2 oz........................	12.2	1.42	....	61.6
with butter, 1 oz..................	0.28	24.09	....	217.9
Beets, 3 oz..........................	1.35	0.09	8.25	39.3
with butter, ½ oz.................	0.14	12.04	....	108.9
String beans, 3 oz..................	1.95	0.27	6.3	35.4
with ground bacon, ½ oz.........	1.49	9.18	....	88.6
Broth	.....	.....	....	.....
Tea	.....	.....	....	.....
Supper				
Lettuce salad:				
Shredder lettuce, 2 oz.............	0.68	0.18	1.64	10.8
Chopped onion, ½ oz.............	0.22	0.04	1.4	6.9
Mayonnaise, 2 oz. (oil, 1½ oz.)..	.....	42.53	....	82.6
Tomato bisque:				
Tomatoes, 1 oz....................	0.34	0.06	1.13	6.4
1 bouillon cube...................	.....	.....	....	.....
Cream, (40%), 2 oz..............	1.24	22.68	1.7	215.8
Hot water to fill bowl............	.....	.....	....	.....
Tea	.....	.....	....	.....
Breakfast				
Bacon, 1 oz........................	2.98	18.37	....	115.7
Egg, 1	6.03	4.72	....	66.6
Cream (18%), 1 oz., for coffee......	0.8	5.6	1.4	59.2
Broth	.....	.....	....	.....
Total	29.70	141.27	21.82	1,415.7

DIABETIC DIET No. 2. EXAMPLE 2

Dinner	Protein, Gm.	Fat, Gm.	Carbohyd., Gm.	Calories
Fish, 1⅔ oz........................	8.41	4.86	....	52.5
with butter, ½ oz.................	0.15	12.75	....	115.4
Cabbage, 2 oz.......................	0.90	0.18	3.18	17.8
with cream (18%), 1 oz..........	0.80	5.60	1.4	59.2
Tomatoes, 3 oz.....................	1.02	0.18	3.39	19.2
with butter, ½ oz.................	0.15	12.75	....	115.4
Broth	.....	.....	....	.....
Tea	.....	.....	....	.....
Supper				
Asparagus, 3 oz....................	1.29	0.09	....	15.5
with mayonnaise, 2 oz. (oil, 1⅔ oz.)	.....	42.53	....	382.6
Lettuce, ⅔ oz......................	0.68	0.17	....	10.8
with bacon, ½ oz.................	1.49	9.18	....	86.6
Custard:				
Cream (18%), 2 oz..............	1.60	11.2	2.8	118.4
2 egg yolks......................	2.71	9.98	....	109.0
Tea	.....	.....	....	.....
Broth	.....	.....	....	.....
Breakfast				
1 egg	6.03	4.72	....	66.6
Spinach, 3 oz......................	1.77	0.27	2.73	20.4
with butter, ½ oz.................	0.15	12.75	....	115.4
Cream (18%), 2 oz., for coffee.....	1.60	11.2	2.8	118.4
Broth	.....	.....	....	.....
Total	28.75	138.42	20.31	1,423.0

DIABETIC DIET No. 3. EXAMPLE 1

Dinner	Protein, Gm.	Fat, Gm.	Carbohyd., Gm.	Calories
Trout, 2 oz........................	10.26	5.84	....	93.6
butter, ½ oz....................	0.14	12.04	....	108.9
Asparagus salad:				
Lettuce. 1 oz....................	0.34	0.09	0.82	5.4
Asparagus, 3 oz.................	1.29	0.09	2.37	15.33
Mayonnaise, 2 oz...............	....	42.53	....	382.6
Celery, 3 oz......................	0.93	0.09	....	15.6
Watermelon, 3 oz................	0.33	0.18	5.07	25.8
Tea	....	....	....	....
Broth	....	....	....	....
Supper				
Tomatoes, 4 oz...................	1.36	1.24	4.52	25.6
with butter, ½ oz...............	0.14	12.04	....	108.9
Egg salad:				
Shredded lettuce, 2 oz..........	0.68	1.18	1.84	10.8
1 hard cooked egg.............	6.03	4.72	....	66.6
Mayonnaise, 2 oz. (oil, 1½ oz.)..	....	42.53	....	382.6
Diabetic jello	1.36	....	4.1	21.8
with whipped cream, 2 oz.......	1.24	22.68	1.7	215.8
Broth	....	....	....	....
Tea	....	....	....	....
Breakfast				
Omelet, 1 egg....................	6.03	4.72	....	66.6
1 egg yolk......................	2.7	5.0	....	54.5
Butter, ½ oz....................	0.14	12.4	....	108.9
Cream (18%), 2 oz., for coffee.....	1.6	11.2	2.8	118.4
Broth	....	....	....	....
Total	34.22	176.21	26.24	1,827.7

DIABETIC DIET No. 3. EXAMPLE 2

Dinner	Gm. Protein,	Gm. Fat,	Gm. Carbohyd.,	Calories
Chicken, 2 oz......................	12.2	1.42	....	61.6
creamed with egg...............	6.03	4.72	....	66.6
18% cream, 2 oz.................	1.6	11.2	2.8	118.4
Beets, 3 oz.......................	1.35	0.09	8.25	39.3
with butter, ½ oz...............	0.14	12.04	....	109.8
String beans, 3 oz.................	1.95	0.27	6.2	34.5
with ground bacon, ½ oz.........	1.49	9.18	....	88.6
Walnuts, ½ oz....................	2.61	9.13	1.84	100.0
Broth	....	....	....	....
Tea	....	....	....	....
Supper				
Cabbage salad:				
Lettuce, ½ oz....................	0.17	0.04	0.41	2.7
Cabbage, 1½ oz.................	0.67	0.13	2.38	13.3
Onion, 1½ oz...................	0.22	0.04	1.4	6.9
Mayonnaise, 2 oz. (oil, 1½ oz.)...	....	42.53	....	382.6
Celery, 1 oz......................	0.3	0.04	0.92	5.2
Tomato bisque:				
Tomatoes, 2 oz..................	0.68	0.12	2.26	12.8
Cream (40%), 2 oz..............	1.24	22.68	1.7	215.8
Hot water to fill bowl.				
Tea	....	....	....	....
Breakfast				
Bacon, 1 oz.......................	2.98	18.37	....	177.2
Lettuce, 2 oz.....................	0.68	0.18	1.64	10.8
with mayonnaise, 2 oz...........	....	42.53	....	382.6
Broth	....	....	....	....
Coffee	....	....	....	....
Total	34.31	174.71	29.8	1,826.6

Diabetic Diet No. 3. Example 3

Dinner	Gm. Protein,	Gm. Fat,	Gm. Carbohyd.,	Calories
Trout, 2 oz........................	10.26	5.84	....	46.8
with butter, 1 oz..................	0.28	24.09	....	217.9
Green onions, 1 oz.................	0.45	0.09	2.8	13.8
Sliced tomatoes, 4 oz..............	1.36	0.24	4.52	25.6
with mayonnaise, 2 oz. (oil, 1½ oz.)	....	42.53	....	382.6
String beans, 3 oz.................	1.95	0.27	6.2	35.4
with ground bacon, ½ oz.........	1.49	9.18	....	88.6
Broth	.....	.....	....	.....
Tea	.....	.....	....	.....
Supper				
Spinach, 3 oz......................	1.77	0.27	2.73	20.4
with butter, ½ oz...............	0.14	12.04	....	108.9
Cabbage, 2 oz......................	0.9	0.18	3.18	17.8
with vinegar, salt and pepper.				
Diabetic custard:				
Cream (18%), 3 oz..............	2.4	16.8	4.2	177.6
Egg yolks, 2....................	4.7	0.9	....	109.0
Broth	.....	.....	....	.....
Tea	.....	.....	....	.....
Breakfast				
Bacon, ⅔ oz.......................	1.98	12.24	....	118.1
1 egg.............................	6.03	4.72	....	66.6
Butter, 1 oz.......................	0.28	24.09	....	217.9
Cream (18%), 1 oz.................	0.8	5.6	1.4	59.2
Broth	.....	.....	....	.....
Total	34.78	167.10	25.03	1,706.2

Diabetic Diet No. 3. Example 4

Dinner	Protein, Gm.	Fat, Gm.	Carbohyd., Gm.	Calories
Boiled ham, 2 oz. (medium fat).....	6.93	16.5	....	176.2
Tomato salad:				
Lettuce, 1 oz.....................	0.34	0.09	0.82	5.4
Tomatoes, 3 oz...................	1.02	0.18	3.39	19.2
Mayonnaise, 2 oz. (oil, 1½ oz.)..	.....	42.53	....	382.6
Onions, 3 oz.......................	1.35	0.27	8.4	41.4
with butter, ½ oz...............	0.14	12.04	....	108.9
Celery, 1 oz.......................	0.31	0.03	0.93	5.2
Coffee	.....	.....	....	.....
Tea	.....	.....	....	.....
Supper				
Asparagus, 4 oz....................	1.72	0.12	3.16	20.4
with butter, 1 oz................	0.28	24.09	....	217.9
Spinach, 4 oz......................	2.86	0.36	3.04	27.2
with bacon, 1 oz.................	1.49	9.18	....	88.6
Diabetic junket:				
Milk, 5 oz......................	2.82	3.39	4.23	58.8
with whipped cream (1⅓ oz.)....	0.83	15.12	1.15	143.8
Broth	.....	.....	....	.....
Tea	.....	.....	....	.....
Breakfast				
Spanish eggs:				
Butter, 1 oz.....................	0.28	24.09	....	217.9
Chopped onion, ½ oz.............	0.22	0.04	1.4	6.9
Tomatoes, 1 oz..................	0.34	0.06	1.13	6.4
Eggs, 2........................	12.06	5.44	....	133.2
Cream (18%), 1 oz., for coffee.....	0.8	5.6	1.4	59.2
Broth	.....	.....	....	.....
Total	33.29	159.13	29.63	1,719.2

CLINICAL CALORIMETRY

XXIX. THE METABOLISM IN TUBERCULOSIS *

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INTRODUCTION

In regard to the dietary of tuberculous patients medical opinion has fluctuated within wide limits. The extent of this fluctuation may be seen by an examination of the data collected by Fisher,[1] regarding the dietaries given patients by ninety-five of the leading sanatoriums of the world. In this list the total number of calories fed daily ranges from a maximum of 5,500 to a minimum of 2,140. The number of grams of protein varies from 60 to 190 per diem. To the practical physician, who is faced with the problem of selecting the best type of dietary to prescribe for tuberculous patients, the problem is quite bewildering. To make the selection it is necessary to know, first, the total energy transformations in such patients and, second, the extent of destruction of protein by the toxins of the disease and the minimum amount of protein which must be given to maintain the patient in nitrogen equilibrium. A search of the literature for this information yields unsatisfactory results because of the meagerness of the data and of the fact that most of the work was done before the advent of the most accurate methods of study.

HISTORICAL

For a very complete and comprehensive compilation of the work done prior to 1903 one may refer to Ott.[2] A great part of this work, in which it appears that the technic used was crude and experimental conditions poorly controlled, will be omittted in our references. Some of it is of great historical interest, as for instance, the work of Nysten[3] carried out in Paris in 1811. By means of a respiratory valve he separated the inspired from the expired air, which he collected in a bladder during a measured period of time. This air was analyzed

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for carbon dioxid by shaking it with lime water (over mercury in a graduated cylinder), the oxygen then being absorbed by phosphorus. Calculation of the energy transformation from the gaseous exchange could not be done at that time, but the physiologic principle is the one most commonly used today.   This work is most significant when one considers that it was contemporary with the development of percussion of the chest by Auenbrugger, and the invention of the stethoscope by Laennec.

Although the physical diagnosis of the disease progressed by leaps and bounds, the next study of the respiratory exchange was not made until by Hannover,[4] who studied the production of carbon dioxid in five patients with phthisis.   The body weight is given and the carbon dioxid per minute.   By assuming an average respiratory quotient of 0.80, we may calculate the daily heat production of these patients as between 1,200 and 2,100 calories per day, and from 26.5 to 40 calories per kilogram of body weight.   In 1878 Moeller[5] studied three poorly nourished patients with phthisis, males weighing from 44 to 45 kg., aged from 24 to 48 years.   The carbon dioxid produced was measured in the Pettenkoffer-Voit apparatus in six hour periods.   These patients all had food and beer, so that the metabolism was not basal. Assuming an average respiratory quotient of 0.80, the daily heat production would be between 1,600 and 1,780 calories, or from 35 to 40 calories per kilogram of body weight.

The first work in which the finding of normal respiratory quotients may be taken as evidence of good technic is that of Loewy,[6] who studied exchange of oxygen and carbon dioxid, minute volume respired and nitrogen excretion at different body temperatures after tuberculin injections, using the Zuntz-Geppert appparatus.   He found that there was only a moderate increase in oxygen consumption in fever and that it was greater with rising than with falling temperatures.   In three of his cases, which were incipient, the minute volume respired increased slightly, but in a fourth case with extensive tuberculosis there was a rather close parallelism between the oxygen consumed and the minute volume.   This observation is one of extreme practical importance, as will be seen later.

In the same year Kraus and Chvostek[7] studied five phthisical patients with a Zuntz-Geppert apparatus.   In some of the cases the

4. Hanover: De quantitate relativa et absolute acidi carbonici ab homine sano et aegroto exhalati, Copenhagen, 1845, p. 82.

5. Moeller: Kohlensäureausscheidung   der   Menschen   bei   verkleinerter Lungenoberfläche, Ztschr. f. Biol. **14**:542, 1878.

6. Loewy, A.:   Stoffwechseluntersuchungen im Fieber und bei Lungenaffectionen, Virchow's Arch. f. path. Anat. **126**:218, 1891.

7. Kraus and Chvostek: Ueber den respiratorischen Gaswechsel im Fieberanfall nach Tuberculininjektion, Wien. klin. Wchnschr. **4**:104, 127, 1891.

respiratory quotients lie beyond the limits of possibility. These are the first investigators to give the height of the patient so that the surface area may be calculated. The conditions were not basal, as the patient was not fasting. However, calculations show that an increase of 39 per cent. in the metabolism increased the minute volume respired from 7,743 c.c. to 10,000 c.c., in a case in which proper quotients were obtained.

Work done by Speck [8] may be mentioned also, since it shows in many cases a marked parallelism between the amount of carbon dioxid produced and the minute volume. The respiratory quotients are either so low or so high as to make the results of doubtful value. Data relative to the amount of food taken and muscular activity are not given. Robin and Binet [9] give mass statistics regarding the minute volume, lung capacity, oxygen consumption and respiratory quotients of 162 phthisical patients. Averages only are given, the methods used are not stated, and there has been no attempt to compare individual patients with normals of the same size, so that the data are not very satisfactory. However, it is of interest to note that the minute volumes respired were from 80 to 110 per cent. greater than those of the normals studied. They also found a consumption of oxygen from 70 to 100 per cent. greater. The respiratory quotients were lower in the tuberculous patients. Lung capacity was also greatly reduced.

Staehelin [10] studied a tuberculous patient during a night sweat in a Jacquet respiration chamber. Food was taken before the observation and the subject was very restless. He concluded, however, that the metabolism was not raised and that sweating had no influence on the total metabolism.

In a recent study of the effect of acetyl salicylic acid on the heat regulation in fever Barbour [11] used three tuberculous subjects. These subjects were studied in a Benedict respiration chamber under basal conditions. The basal metabolism in these three cases was only from 3 to 4 per cent. above the average normal.

The absorption of food in tuberculosis has been studied by Blumenfeld,[12] who found that the percentage losses of nitrogen and fat in the stools were within normal limits. However, in certain cases there was marked interference with absorption. Biedert [13] reported a case

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8. Speck: Physiologie des menschlichen Athmens, 1892.

9. Robin and Binet: Bull. méd. Par. **15**:249, 1901.

10. Staehelin, R.: Der respiratorische Gaswechsel eines Phthisikers während des Nachtschweisses, Ztschr. f. klin. Med. **66**:241, 1908.

11. Barbour, Henry G.: Arch. Int. Med. **24**:624 (Dec.) 1919.

12. Blumenfeld, F.: Ueber die diaetetische Verwerthung der Fette bei Lungentuberculose, Ztschr. f. klin. Med. **28**:417, 1895.

13. Biedert: Die Tuberculose des Darms und des lymphatischen Apparats, Jahr. f. Kinderh. **21**:172, 1884.

TABLE 1.—Alcohol Checks for 1916-17

Date and Per Cent. of Alcohol by Weight	Hour	Alcohol Burned, Gm.	Heat Theory, Cal.	Heat Found, Cal.	Heat Error, per Cent.	Oxygen Theory, Gm.	Oxygen Found, Gm.	Oxygen Error, per Cent.	Carbon Dioxid Theory, Gm.	Carbon Dioxid Found, Gm.	Carbon Dioxid Error, per Cent.	Water Theory, Gm.	Water Found, Gm.	Water Error, per Cent.	R. Q. Theory 0.667
5/17/16 92.92	1	13.49	87.63	87.20	−0.5	25.80	26.35	+2.1	23.65	23.34	−1.3	15.47	16.09	+4.0	0.644
	2	13.26	87.23	87.41	+0.2	25.69	24.75	−3.7	23.55	23.34	−0.9	15.40	15.91	+3.3	0.686
	3	13.72	90.26	89.24	−1.1	26.58	26.29	−1.1	24.36	23.90	−1.9	15.93	16.26	+2.1	0.661
Average	...	.....	88.37	87.94	−0.5	26.02	25.80	−0.8	23.85	23.59	−1.1	15.60	16.09	+3.1	0.665
10/3/16 92.92	1	12.05	79.27	82.02	+0.9	23.34	23.81	−0.1	21.40	21.42	+0.1	13.99	15.14	+8.2	0.668
	2	12.78	84.07	86.45	+2.8	24.76	25.05	+1.2	22.69	22.57	−0.5	14.84	15.76	+6.2	0.655
Average	...	.....	81.67	84.24	+3.1	24.05	24.18	+0.5	22.05	22.00	−0.2	14.42	15.45	+7.2	0.662
10/10/16 92.92	1	12.83	84.41	83.51	−1.1	24.85	24.98	+0.3	22.78	22.42	−1.6	14.90	15.27	+2.5	0.654
	2	13.16	86.57	87.08	+0.6	25.49	24.94	−2.2	23.37	23.42	+0.2	15.28	15.79	+3.3	0.683
	3	13.36	87.89	85.42	−2.8	25.88	25.88	0.0	23.72	23.39	−1.4	15.51	15.76	+1.6	0.657
Average	...	.....	86.29	85.34	−1.1	25.41	25.25	−0.6	23.29	23.08	−0.9	15.23	15.61	+2.5	0.665
12/4/16 92.92	1	11.97	78.75	80.57	+2.3	23.19	22.63	−2.4	21.25	20.92	−1.6	*33.90	31.40	−7.4	0.672
	2	11.68	76.84	77.80	+1.2	22.63	22.37	−1.4	20.74	20.78	+0.2	33.57	30.89	−8.0	0.676
	3	11.33	74.54	76.88	+3.1	21.95	21.21	−3.4	20.12	19.67	−2.2	33.16	30.63	−7.6	0.674
Average	...	.....	76.71	78.42	+2.2	22.59	22.07	−2.3	20.70	20.46	−1.2	33.54	30.97	−7.2	0.674
2/28/17 92.44	1	11.94	78.14	78.15	0.0	23.01	22.66	−1.5	21.09	20.61	−2.3	13.85	14.39	+8.9	0.662
	2	11.91	77.95	78.32	+0.5	22.95	22.18	−3.4	21.04	21.09	+0.2	13.83	13.62	−1.5	0.691
	3	12.12	79.32	80.64	+1.7	23.36	23.13	−1.0	21.41	21.19	−1.0	14.06	14.37	+2.2	0.666
Average	...	.....	78.47	79.04	+0.7	23.11	22.66	−2.0	21.18	20.96	−1.0	13.91	14.13	+1.6	0.673
4/23/17 92.44	1	12.62	82.59	82.93	+0.4	24.32	23.01	−5.4	22.29	21.47	+3.7	14.64	14.58	−0.4	0.678
	2	11.39	74.54	75.36	+1.1	}21.95{	46.92	−1.8	}20.12{	42.92	−2.0	}13.22{	}13.88{	+1.8	0.665
	3	13.40	87.00	87.98	+0.3	25.82			23.67			15.55	15.45		
Average	...	.....	81.61	82.09	+0.6	24.03	23.31	−3.0	22.03	21.46	−2.6	14.47	14.62	+0.6	0.669
Totals	...	.....	1397.70	1406.96	+0.7	411.57	405.61	−1.4	377.25	372.45	−1.3	307.10	305.14	−0.6	0.668

* 20 gm. extra water introduced.

of fat diarrhea in a child with tuberculosis of the intestine, mesenteric lymph nodes and peritoneum. Also Friederich Mueller[14] found a loss of 32.9 per cent. of fat and 7.9 per cent. of nitrogen in the stools of a patient with tuberculous ulcers in the intestine and marked amyloidosis which involved the liver very slightly and the pancreas not at all.

The question of the toxic destruction of protein has received much attention. An excellent compilation of this work, with abundant quotations of experimental data, may be found in Ott.[2] The general results of this work tend to show that in the afebrile condition many phthisical patients will readily make large gains in nitrogen. With febrile patients, either with spontaneous fever or with fever following tuberculin injections, small losses of nitrogen occur on diets furnishing about 2,500 calories and from 100 to 150 gm. of protein per diem. These small nitrogen losses would become important only because of the long duration of the disease. The determination of the protein minimum in tuberculosis does not seem to have been made, although it has been the subject of some speculation.

The discussion of the nitrogen losses in phthisis would be incomplete without mention of loss in the sputum. Lanz[15] estimated the daily nitrogen loss in the sputum of sixteen patients with phthisis. The protein loss was calculated from the total nitrogen of the sputum and varied from 1.69 to 7.00 gm. of protein per diem.

METHODS OF STUDY

The respiration calorimeter of the Russell Sage Institute of Pathology was employed. This apparatus has been previously described in Paper 2 of this series.[16] The technic has been essentially that described in Paper 4 of the series,[17] with the few exceptions noted below. Patients were studied 14 to 16 hours after the last regular meal, though each received the small standard breakfast described in Paper 26 of this series.[18] The only effect of this meal was found to be an increase in the metabolism of 2 per cent. in the third hour

14. Mueller, Fr.: Untersuchungen über Icterus, Ztschr. f. klin. Med. **12**:86, 1887.

15. Lanz: Deutsch. Arch. f. klin. Med. **56**:619, 1896.

16. Riche, J. A., and Soderstrom, G. F.: The Respiration Calorimeter of the Russell Sage Institute of Pathology in Bellevue Hospital, Arch. Int. Med. **15**:805 (June) 1915.

17. Gephart, F. C., and Du Bois, E. F.: The Determination of the Basal Metabolism of Normal Men and the Effect of Food, Arch. Int. Med. **15**:835 (June) 1915.

18. Soderstrom, G. F., Barr, D. P., and Du Bois, E. F.: The Effect of a Small Breakfast on the Heat Production, Arch. Int. Med. **21**:613-620 (May) 1918.

TABLE 2.—ALCOHOL CHECKS FOR 1919-20

Date and Per Cent. of Alcohol by Weight	Hour	Alcohol Burned, Gm.	Heat			Oxygen			Carbon Dioxid			Water			R. Q. Theory 0.667
			Theory, Cal.	Found, Cal.	Error, per Cent.	Theory, Gm.	Found, Gm.	Error, per Cent.	Theory, Gm.	Found, Gm.	Error, per Cent.	Theory, Gm.	Found, Gm.	Error, per Cent.	
12/5/19 89.4	1	12.87	81.45	81.16	−0.3	23.99	23.85	−0.1	21.99	21.62	−1.7	14.86	15.18	+2.2	0.659
	2	12.53	79.30	81.48	+2.7	23.35	23.31	0.0	21.40	21.40	0.0	14.47	14.96	+3.4	0.668
	3	12.63	79.91	79.83	0.0	23.53	22.98	−2.6	21.57	21.23	−1.6	14.58	14.92	+2.3	0.673
	4	12.64	80.00	77.78	−2.8	23.56	23.02	−2.3	21.59	20.77	−0.4	14.60	14.90	+2.1	0.657
Average	...	.....	80.17	80.06	−0.1	23.61	23.28	−1.4	21.64	21.26	−1.3	14.63	14.99	+2.5	0.664
2/26/20 89.4	1	11.15	70.54	71.91	+1.9	20.77	19.96	−3.9	19.04	18.54	−2.6	12.87	13.22	+2.7	0.675
	2	10.84	68.58	68.14	−0.6	20.19	21.39	+5.9	18.51	17.74	−4.2	12.52	12.73	+1.7	0.603
	3	11.21	70.95	71.75	+1.2	20.89	20.45	−2.1	19.15	18.65	−2.9	12.95	13.28	+2.5	0.663
Average	...	.....	70.02	70.60	+0.8	20.62	20.60	−0.1	18.90	18.31	−3.1	12.78	13.08	+2.3	0.646
2/28/20 89.4	1	10.98	69.47	69.11	−0.5	20.45	20.30	−0.7	18.75	18.08	−3.5	12.68	13.58	+7.1	0.648
	2	10.67	67.52	68.38	+1.3	19.88	20.14	+1.3	18.22	17.21	−5.5	12.32	13.32	+8.1	0.621
	3	10.31	65.23	66.57	+2.1	19.21	19.02	−1.0	17.61	16.47	−6.5	11.90	12.94	+8.7	0.630
Average	...	.....	67.41	68.02	+0.9	19.85	19.82	−0.2	18.19	17.25	−5.2	12.30	13.28	+8.0	0.633
3/15/20 89.4	1	11.66	73.81	74.30	+0.7	21.73	19.22	−11.5	19.92	19.67	−1.3	13.47	14.07	+4.5	0.745
	2	11.31	71.56	71.29	−0.4	21.07	20.44	−3.0	19.31	18.92	−2.0	13.06	13.30	+1.8	0.673
	3	11.15	70.56	71.90	+1.9	20.78	21.08	+1.2	19.04	18.74	−1.6	12.88	13.63	+5.8	0.648
	4	11.19	70.80	71.13	+0.5	20.84	20.80	−0.2	19.11	18.54	−3.0	12.92	13.34	+3.3	0.648
Average	...	.....	71.68	72.16	+0.7	21.11	20.37	−3.5	19.35	18.97	−2.0	13.08	13.59	+4.0	0.677
3/18/20	1	11.70	72.96	75.22	+3.1	21.48	21.25	−1.1	19.69	19.47	−1.1	13.49	13.84	+2.6	0.666
3/22/20 88.1	1	12.64	78.80	82.69	+4.9	23.20	22.35	−3.7	21.27	20.85	−2.0	14.57	15.11	+3.7	0.678
	2	12.22	76.22	80.18	+5.2	22.44	22.20	−1.1	20.57	20.34	−1.1	14.09	14.60	+3.6	0.666
	3	12.27	76.51	79.60	+4.0	22.53	22.19	−1.5	20.65	20.09	−2.7	14.15	14.66	+3.6	0.659
Average	...	.....	77.18	80.82	+4.7	22.72	22.25	−2.1	20.83	20.43	−1.9	14.27	14.79	+3.6	0.668
5/6/20 88.1	1	12.27	76.53	77.41	+1.2	22.53	22.24	−1.3	20.66	20.11	−2.7	14.15	14.64	+3.5	0.658
	2	11.89	74.15	74.88	+1.0	21.83	21.21	−2.8	20.01	19.49	−2.6	13.71	14.29	+4.2	0.668
	3	11.88	74.09	75.64	+2.1	21.82	21.76	−0.3	20.00	19.67	−1.7	13.70	14.29	+4.3	0.658
Average	...	.....	73.92	75.98	+2.8	22.06	21.73	−1.5	20.22	19.76	−2.3	13.85	14.41	+4.0	0.661
Totals......	...	.....	1548.94	1570.35	+1.4	456.07	449.06	−1.5	418.06	407.60	−2.5	283.94	298.80	+5.2	0.660

after eating. As a rule the observations were started in the latter part of the third hour or early in the fourth hour.

In the direct calorimetric calculation of the heat lost from or stored in the body, the rectal temperature was used, taking the specific heat only of the body at 0.83. This figure has been found to give fairly accurate results in a considerable series of normal subjects. At best, however, it can be considered as merely an average figure. For different individuals it must vary considerably, depending on the proportions of the various tissues in the body, especially of fat (specific heat = 0.45) and water (specific heat = 1).[19] Moreover, even though the specific heat is not known exactly, it may be considered to remain constant during short periods. The body weight for short periods is likewise a constant. With this in view, a comparison in each hour of the heat production (calculated from the respiratory exchange) with the heat elimination (measured directly) will show that the change in the rectal temperature does not always parallel that of the average body temperature.

The surface area in each case was determined from the height and weight by the "height-weight chart" of Du Bois and Du Bois.[20] In calculating the variations of the metabolism from the average normal, based upon the surface area, the normal heat production per square meter of body surface has been taken from the table given by Aub and Du Bois,[21] which takes into account the effect of age. If the predictions of the normal metabolism for each individual in the series based upon the figures of Aub and Du Bois are compared with the predictions for the same individuals made from Benedict's tables [22] the average difference between the two predictions will be found to be about 3 per cent.

ALCOHOL CHECKS

Interspersed throughout the series were a number of alcohol checks. The first four cases of the series were studied in 1917. The alcohol checks for that period are to be found in Table 1. As the calorimeter had not been in use during the war it was necessary to make quite a number of checks before the apparatus was finally put in good condition. A satisfactory check was first obtained on Dec. 5, 1919, so

19. Rubner, M.: Kalorimetrie, Tigerstedt's Handb. d. physiologische Methoden, Hirzel, Leipzig, 1911, **1**:170, Part. 3.

20. Du Bois, Delafield, and Du Bois, E. F.: A Formula to Estimate the Approximate Surface Area if Height and Weight be Known, Arch. Int. Med. **17**:863 (June) 1916.

21. Aub, J. C., and Du Bois, E. F.: The Basal Metabolism of Old Men, Arch. Int. Med. **19**:823 (June) 1917.

22. Harris, J. A., and Benedict, F. G.: A Biometric Study of the Basal Metabolism in Man, Carnegie Int. Wash., 1919, Pub. 279.

that patients were not studied until after that date. The results of the alcohol checks for 1919-1920 are given in Table 2.

During all of the previous work with the calorimeter a special soda lime was used.[23] This same soda lime was used up to Feb. 12, 1920. At this time a new soda lime, which had been devised for use in submarines, was introduced. This product contained relatively little sodium hydroxid and, consequently, the water formed in the reaction with carbon dioxid was not held in the soda lime but passed off rapidly into the sulphuric acid of the last absorber in the train. The efficiency of this latter absorber was not great enough to handle all of this moisture. The result is seen in examining the alcohol checks for February 26 and 28, and March 15. In these checks the carbon dioxid found was too low, while the results for oxygen consumed and for heat check fairly well. The effect of this error is to give respiratory quotients which are too low. The results for the direct calorimetry are quite satisfactory, and the error in the indirect calorimetry is small, since the indirect calculation is based on the oxygen, for which better checks were obtained.

After March 15, 1920, the Stanley Jordan soda lime was again used, the checks for March 18 and 22 being satisfactory for the purpose of this study.

<div align="center">REPORT OF CASES [24]</div>

CASE 1.—Charles G. *Tuberculosis of pleurae and peritoneum.*

History.—A laborer, 31 years of age, born in the United States, was admitted to the service of Dr. Charles Nammack in Bellevue Hospital April 13, 1917, and discharged unimproved June 3, 1917.

September, 1916, he had pleurisy with effusion on the left side. March 12, 1917, he began to feel pain, localized to a small area in the epigastrium. He had much flatulence. Five days later he noticed that his abdomen was swollen. He had been constipated and the pain had steadily increased in intensity. He had severe night sweats but no cough.

Physical Examination.—Patient was a poorly developed, emaciated negro; height 165 cm.; weight 52.4 kg. The tongue showed a white coat. There were signs of fluid on the right side of the chest to one inch below the spine of the scapula and, on the left, to the angle of the scapula. There was harsh breathing, with many râles above the level of the fluid. The heart was overacting. The rate was rapid, 120 or more, when the patient was in dorsal decubitus. The abdomen was tense and offered a boggy resistance to palpation. There was dulness in both flanks and a distinct fluid wave.

Laboratory Examination.—Urine showed a trace of albumin, hyaline and granular casts. The sputum was examined but no tubercle bacilli were found. Usually his cough was unproductive. The roentgenogram showed pleural effusion on both sides, but no lung involvement.

April 14, in the general ward, the abdomen was tapped and 3,800 c.c. of cloudy, blood-tinged fluid were removed. A guinea-pig, injected with this

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23. Made by the Stanley Jordan Company, New York.

24. The first four cases were studied by D. P. Barr in 1917; the remainder by W. S. McCann in 1919-1920.

fluid, died of intercurrent infection April 30, showing no sign of tuberculosis. April 23 the right chest was tapped and 1,500 c.c. of cloudy, straw-colored fluid were removed.

May 7 he was admitted to the metabolism ward. He was observed in the calorimeter May 8, 11 and 14. With temperature varying from 37.8 to 38.1 C., his basal metabolism was 13 per cent. above the average normal. His right chest was tapped a second time May 15 and 400 c.c. of thick, bloody fluid were withdrawn. While in the ward he ran a remittent temperature. The symptoms remained unchanged. He maintained his weight and had an excellent appetite. June 3 he was discharged unimproved.

TABLE 3.—DIET CHART AND NITROGEN BALANCE IN CASE 1

Name and Date	Food			Food N, Gm.	Urine N, Gm.	Feces N, Gm. (Estimated)	Excreta N, Gm.	N Balance, Gm.	Body Weight, Kg.
	Total Calories	Carbohydrate, Cals.	Fat, Cals.						
Charles G.									
5/ 8/17	2,247	925	981	13.3	12.5	1.3	13.8	−0.5	53.1
5/ 9/17	2,233	967	889	14.7	11.2	1.5	12.7	+2.0	
5/10/17	2,179	908	909	14.1	11.2	1.4	12.6	+1.5	52.5
5/11/17	2,225	860	1,006	14.0	12.5	1.4	13.9	+0.1	
5/12/17	2,668	1,017	1,257	15.4	13.4	1.5	14.9	+0.5	
5/13/17	2,733	1,110	1,229	15.4	13.5	1.5	15.0	+0.4	53.5
5/14/17	1,575	636	686	10.0	9.0	1.0	10.0	0.0	
5/15/17	2,639	1,159	1,082	15.5	13.6	1.6	15.2	+0.3	53.7
5/16/17	2,614	1,057	1,166	15.3	11.9	1.5	13.4	+1.9	
5/17/17	1,580	899	595	3.4	8.3	1.0	9.3	−5.9	53.0
5/18/17	2,637	1,383	1,167	3.4	8.3	1.0	9.3	−5.9	53.2
5/19/17	2,635	1,280	1,268	3.4	4.9	1.0	5.9	−2.5	53.7
5/20/17	2,575	1,269	1,221	3.3	4.5	1.0	5.5	−2.2	52.4
5/21/17	2,548	1,261	1,211	3.0	5.0	1.0	6.0	−3.0	52.7
5/22/17	2,400	1,061	1,255	3.3	5.1	1.0	6.1	−2.8	52.8
5/23/17	2,091	947	1,072	2.8	4.3	1.0	5.3	−2.5	52.2
5/24/17	2,635	1,114	1,136	15.0	8.2	1.5	9.7	+5.3	52.5
5/25/17	2,875	1,482	1,300	3.6	5.9	1.0	6.9	−3.3	52.6
5/26/17	2,973	1,705	1,189	3.1	5.2	1.0	6.2	−3.1	52.6
5/27/17	2,951	1,690	1,185	3.0	4.4	1.0	5.4	−2.4	52.7
5/28/17	2,725	1,421	1,224	3.1	4.8	1.0	5.8	−2.7	52.9
5/29/17	3,167	1,950	1,142	2.9	4.7	1.0	5.7	−2.8	52.1
5/30/17	3,138	1,886	1,178	2.9	4.7	1.0	5.7	−2.8	52.4
5/31/17	3,019	1,826	1,106	3.4	5.0	1.0	6.0	−2.6	52.1
6/ 1/17	2,905	1,570	1,260	2.9	4.9	1.0	5.9	−3.0	

CASE 2.—Trellis H. *Tuberculosis of lungs and lymph nodes.*

History.—A waiter, 24 years of age, born in the United States, was admitted to the service of Dr. Robert J. Carlisle May 3, 1917, and discharged unimproved May 22, 1917. The history was not satisfactory because of the very limited intelligence of the patient. In 1913 he had empyema, for which he was treated at the Presbyterian Hospital in Chicago.

April 15 he noticed for the first time a mass beneath the chin on the left side, which grew rapidly. About two weeks later he found that a similar, smaller mass had appeared on the right side. He had had an occasional dry, tickling cough, but no night sweats.

Physical Examination.—Patient was a poorly developed, poorly nourished boy, mentally deficient, height 168 cm., weight 51.6 kg. The teeth showed a marked pyorrhea and were in very bad condition. In the submental region and at the angles of the jaw there were large, hard, semi-elastic, painless masses. The swelling at the angle of the jaw on the right side was hot and showed slight fluctuation. There was a chain of very hard, discrete glands in the right groin; another of similar character in the left axilla.

Lungs: At both apices anteriorly and posteriorly there was dulness to percussion. There was high pitched, almost tubular breathing over the left apex posteriorly and there were a few subcrepitant rales over the right apex.

Laboratory Examination.—The urine was negative. Blood: Leukocytes, 8,200; polymorphonuclears, 69 per cent.; erythrocytes, 4,400,000; hemoglobin, 75 per cent. Wassermann negative. Von Pirquet positive. The roentgenogram showed marked peribronchial infiltration in the left upper lobe between the first and third ribs. The sputum was repeatedly examined, but no tubercle bacilli were found.

May 9: Basal metabolism, with temperature from 40.1 to 40.2 C., was 29 per cent. above the average normal, and with temperature between 39.7 and 40.1 C., it was 43 per cent. above the average normal, due, in part, to coughing.

His condition did not change while in the hospital. His temperature was irregular. May 22 he was transferred to a tuberculosis sanitarium.

Case 3.—Robert W. *Pleurisy with effusion.*

History.—A ship's carpenter, 39 years of age. He was admitted April 23, 1917, and discharged improved on June 2, 1917. He had been in the Navy for eight years. For the past six years he had been on mercantile vessels. In 1900 he had pneumonia, with which he was ill for one month. He had always been a very heavy drinker. He denied venereal disease.
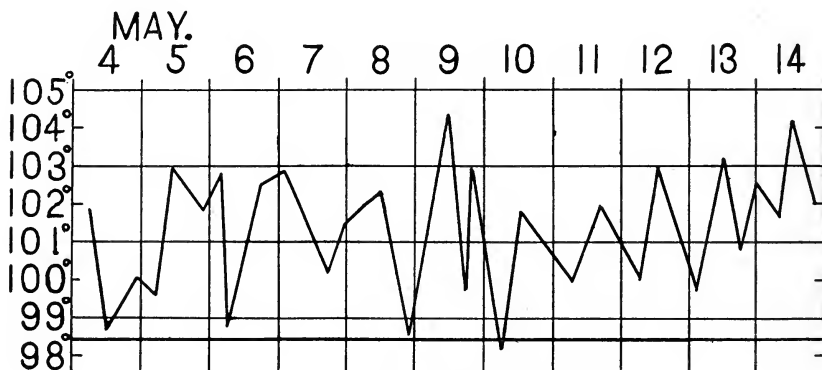
Fig. 1.—Temperature chart of Trellis H.

April 13 he began to feel short of breath, coughed frequently and had some pain in the epigastrium and along the sternum. Coughing or deep breathing increased the pain.

Physical Examination.—Patient was a well developed, rather emaciated man who showed a moderate degree of cyanosis, height 165 cm.; weight 53.4 kg. Lungs: There was absence of fremitus, flatness on percussion, distant voice and distant bronchovesicular breathing over the entire left lung. The right lung was normal. Heart: Was pushed to the right. The right border was 8 cm. to the right of the midsternal line. The left border of dulness merged with flatness of fluid. Coughing was unproductive.

Physical Examination.—One sample of sputum was obtained, but contained no tubercle bacilli. Urine: negative. Blood: Leukocytes, 8,400; polymorphonuclears, 64 per cent.; lymphocytes, 27 per cent. Roentgenogram showed pleurisy with effusion on the left side, but indicated no lung involvement.

April 24, 1,400 c.c. of straw-colored fluid were removed from the left chest. No tubercle bacilli were found. April 26, after 2,000 c.c. had been withdrawn, there were still signs of fluid. May 3 the chest was again filled with fluid, 3,500 c.c. of which were withdrawn. May 15 the level of the fluid was from the middle of the scapula behind to the third rib in front. May 17 1,400 c.c. were withdrawn, after which the level of fluid was at the eighth rib in the midscapular line. May 25 at 8:15 a. m. he had a chill, the cause of which was

not apparent. On the same day, from 10:30 a. m. to 2:30 p. m., he was observed in the calorimeter, temperature falling from 40.10 to 39.36 C., metabolism 29 per cent. above the average normal.

He was in the calorimeter May 28 while the temperature was normal. In the course of this observation, however, he was seized with abdominal pain. During the rest of the day he had a diarrhea, and passed fourteen stools which contained much blood and mucus. This continued until May 31. Careful examination of the centrifugalized stools revealed no tubercle bacilli. June 2 he was discharged from the hospital. His temperature was normal. The signs of fluid did not change after May 17.

CASE 4.—George P. *Acute miliary tuberculosis; tuberculoma of left eye.*

History.—A laborer, 18 years of age, born in Greece, was admitted April 23, 1917, and discharged June 12, 1917. He came to this country from Greece in January, 1917. He had never had any serious illness.

The latter part of March, 1917, he lost his appetite, felt feverish, and had several night sweats. A few days later he found that he could not see with his left eye. He had coughed continually since the onset of the trouble, and for a month had sharp, stabbing pain in the left side of the chest. Since he came to this country he had lost twenty-five pounds in weight, dropping from 154 to 129 pounds.
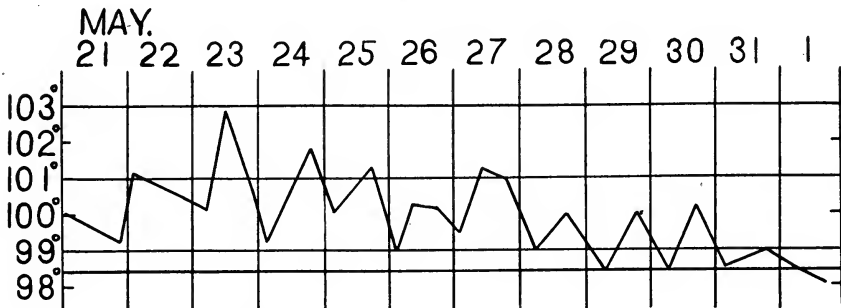
Fig. 2.—Temperature chart of Robert W.

Physical Examination.—Patient was a well developed, moderately emaciated boy, height 172 cm., weight 58.5 kg. His face showed a high color and his vasomotor system was very unstable. The eyes were normal externally. The retina of the right eye was normal. In the left retina there was a tumor, white in color, above and to the temporal side of the optic disk, about two disks in width, three disks in length. It was elevated six diopters above the surrounding retina. There was a small hemorrhage into the retina on the temporal side of the tumor. Lungs: There was a dulness to percussion and prolonged, high pitched, bronchial breathing at the right apex posteriorly. Anteriorly there were many constant, fine râles. At the left base there were many coarse, leathery friction râles. The cervical, axillary and inguinal lymph nodes were palpable.

On later examination, April 22, the tumor in the left retina was found to be elevated eleven diopters and to have spread to involve the optic disk.

Laboratory Examination.—Urine: negative. Blood: Leukocytes, 7,000; polymorphonuclears, 70 per cent.; erythrocytes, 3,600,000. Tuberculosis fixation test was positive. Questionable tubercle bacilli were found once in the sputum. The roentgenogram showed a diffuse miliary tuberculosis with a cavity at the right apex.

May 24, he was observed in the calorimeter; temperature varied from 37.5 to 37.8 C.; basal metabolism, 11 per cent. above the average normal.

The cough and pain in the chest continued and were very troublesome. With the exception of the rapid growth of the tuberculoma in the left eye, his condition changed very little after admission to the hospital. He was sent to a tuberculosis sanitarium June 12.

TABLE 4.—DIET CHART AND NITROGEN BALANCE IN CASE 4

Name and Date	Total Food, Cals.	Carbo-hydrate, Gm.	Fat, Gm.	Food N, Gm.	Excreta N,* Gm.	N Balance, Gm.	Body Weight, Kg.
George P.							
5/24/17	1,800	208	72	10.6	10.0	+0.6	58.6
5/25/17	2,500	241	120	15.1	11.8	+3.3	58.6
5/26/17	2,530	236	125	15.6	13.4	+2.2	58.1
5/27/17	2,530	242	122	15.8	17.4	—1.6	58.5
5/28/17	2,580	283	110	15.0	15.1	—0.1	
5/29/17	2,930	420	122	2.9	10.2	—7.3	58.4
5/30/17	3,140	458	127	3.0	6.4	—3.4	
5/31/17	3,040	449	119	3.5	5.5	—2.0	59.2
6/ 1/17	2,960	395	136	3.1	5.1	—2.0	
6/ 2/17	2,380	283	123	2.9	4.2	—1.3	58.1
6/ 3/17	2,600	336	123	3.1	5.0	—1.9	
6/ 4/17	2,700	346	128	3.4	4.8	—1.4	58.1

* Fecal nitrogen estimated.

CASE 5.—Spencer C. *Pulmonary tuberculosis, both lungs, with cavitation.*

History.—A negro, aged 46 years, was admitted Dec. 8, 1919, complaining of shortness of breath, weakness and cough. One brother had died of tuberculosis. The patient's early life had been spent under poor conditions, but his health had been good up to 1916 when he was discharged from the army. Since then his occupation had been that of janitor. During the last two years he had continually "felt below par," progressively losing weight and strength. During this time he had a chronic cough which was worse at night and frequently kept him from sleeping. The cough became productive of a tenacious, greenish sputum in which he had never noted the presence of blood. During the year before admission, the wasting progressed rapidly, so that he was sixty-five pounds below his best weight (163 pounds). He had occasional night sweats. In the past few months he had noted increasing shortness of breath, at first only on exertion, but later while lying in bed. His cough had become so severe as to induce vomiting. One month before admission he had dull pains all over the chest, but these had disappeared. His appetite was whimsical. Bowels were constipated.

Physical Examination.—Patient was a fairly well developed, emaciated negro, lying flat in bed but showing considerable dyspnea, height 169 cm., weight 44.4 kg. Lips showed some cyanosis. Facies showed exhaustion and lethargy. Eyes were very prominent, with considerable bulging of the periocular tissues. The few remaining teeth were carious. The tonsils were markedly enlarged and cryptic. On both sides of the neck there were numerous, enlarged lymph nodes about the size of a bean. Thorax: showed retractions above and below both clavicles. The expansion was poor, but more limited on the right side. Lungs: showed impaired resonance over the entire chest, more marked on the right side. On auscultation bronchial breathing was heard over both upper lobes, with many medium and coarse râles heard over the entire chest. Near the inner end of the spine of the right scapula posttussive suction was heard. Heart: not enlarged. The first sound was of poor quality, the pulmonary second sound was accentuated. Rhythm was regular, but the rate was very rapid. Arteries: thickened but not tortuous.

Blood Pressure: Systolic, 115 mm.; diastolic, 65 mm. Abdominal findings: negative. Lymph nodes: enlarged in neck, axillae, inguinal and epitrochlear regions. Genitalia: normal. Fingers and toes: showed marked clubbing. There was slight edema of the ankles. Reflexes: Achilles and patellar reflexes not obtained.

Laboratory Examination.—The sputum showed numerous tubercle bacilli. Urine: normal, except for low specific gravity. Roentgenogram of chest showed diffuse peribronchial infiltration of the entire right lung, with numerous small cavity formations at the right apex. Numerous foci of peribronchial infiltration scattered irregularly throughout the central portion of the left lung. The temperature course is shown in Figure 3.

The patient was observed in the calorimeter December 10, the basal metabolism being 12 per cent. above the average normal for his surface area during a period of normal temperature.

Patient left hospital two days later and subsequent history is unknown.

CASE 6.—Edith B. *Pulmonary tuberculosis, both lungs, with cavitation.*

History.—Colored female, aged 20 years, admitted Dec. 12, 1919, complaining of pain in the left side of chest, cough and weakness. One aunt died of
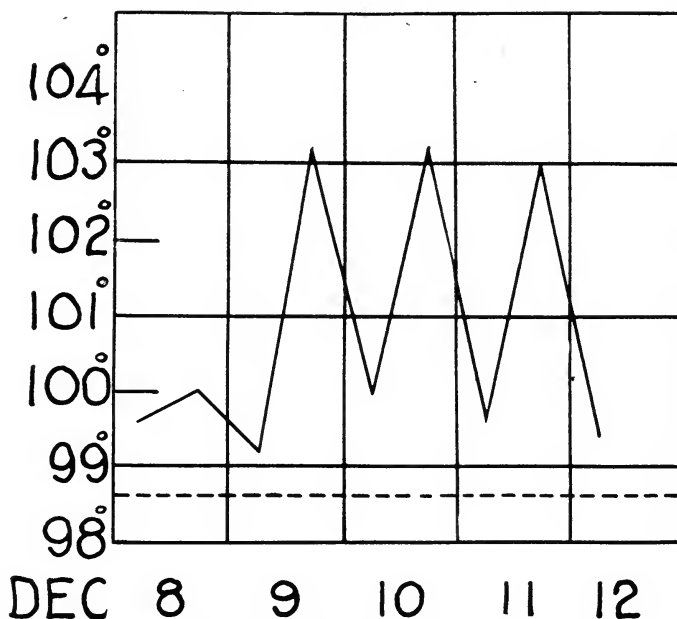
Fig. 3.—Temperature chart of Spencer C.

tuberculosis. Her mother had a disease of the spine with partial paralysis of one leg. The patient had been married eighteen months but had had no pregnancies. In childhood she had whooping cough and measles. In 1916 she had pneumonia. Otherwise her health had been good up to the onset of the present illness. Her normal weight was 135 pounds.

Early in September, 1919, patient became very weak and dizzy about 4 p. m., and at this time she felt chilly. Soon after this she developed a troublesome cough which was much worse at night. She expectorated a moderate amount of mucoid sputum in which no blood was noticed. At this time she was engaged in nursing an aunt who died one month later of consumption. A little later she began to have a great deal of pain in the left side of the chest on coughing and on deep breathing. These symptoms continued to grow worse until she was confined to bed most of the day. Her appetite was very poor. She lost weight, from 135 to 109 pounds. She had "hot fevers" at night, followed by sweats. She was admitted to the service of Dr. James Alexander Miller, through whose kindness she was transferred for study.

Physical Examination.—The patient was a young negro woman, 178 cm. tall, weighing 44.6 kg., alert and intelligent, lying on her side in bed, breathing rapidly and coughing occasionally. Mucous membranes were pale and not cyanotic. Thorax: well formed, but with moderate retractions above and below clavicles, most marked on the left side, involving the second and third interspaces. The expansion of the right side of the chest was fairly free, but there was marked limitation of motion of the left side. Lungs: Percussion note was resonant at both bases, but there was no excursion at the left, while at the right base there was an excursion of 5 cm. Both apices were dull both front and back, more marked on the left. There was diminution of the voice and breath sounds at the left base behind, and over the dull areas the breathing was bronchovesicular or bronchial in character, with many fine râles. Heart: Apex impulse could not be located. The cardiac dulness extended 12 cm. to the left in the fifth intercostal space, but the right border could not be sharply located. Rate rapid; rhythm regular. No murmurs heard. Pulse: rapid and of low tension. Arteries: normal. Abdomen: negative. Genitalia: not examined. Extremities: normal. Reflexes: normal. Epitrochlear lymph nodes: enlarged.

Laboratory Examination.—Sputum contained many tubercle bacilli. Urine: normal. Roentgenogram of chest showed infiltration, fibrosis and cavitation of the middle portion of the right lung and the entire left lung with the exception of a small portion of the left base. Cavity formation was located in the upper
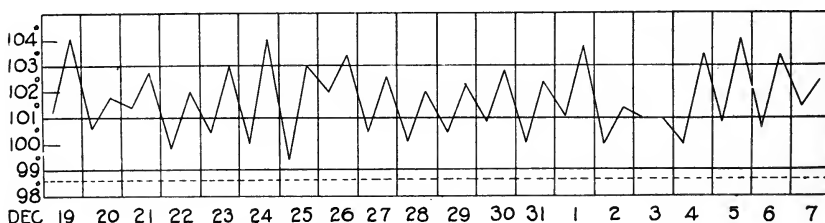
Fig. 4.—Temperature chart of Edith B.

portion of the middle lobe, but there were also numerous small cavities in the left lung. There were many pleuropericardial adhesions, with marked distortion of the cardiac outline. Compensatory emphysema in the right lung and fibrosis in the left lung.

Observations were made in the calorimeter December 7 and 19 and January 6. The first observation made at normal temperature showed no elevation of the basal metabolism. Subsequent observations during high fever, with coughing, raised the metabolism from 18 to 20 per cent. above the average normal and still further increases were due to restlessness during the third observation. The mechanism of temperature regulation in this case is shown graphically in Figure 14.

Case 7.—Harry G. *Pulmonary tuberculosis, extensive bilateral infiltration.*

History.—A fountain-pen maker, 18 years of age, was admitted Jan. 2, 1920. complaining of cough, weakness and night sweats. He had measles in childhood, but was well and active, though rather weak as a boy. At the age of 16 he went to work in a fountain-pen factory, where the work was confining and the atmosphere full of dust. His appetite was poor, bowels constipated, but he had no respiratory symptoms until November, 1919.

At that time he caught cold and began to have a racking cough with a moderate amount of viscid sputum. The cough reached its maximum intensity one month before admission, after which it was less troublesome. It was most severe at night, when it sometimes produced vomiting. He had night sweats

before entering the hospital, but none during his stay. Two weeks before admission he coughed up about one teaspoonful of bright blood. He had become very constipated. He had no urinary symptoms. His greatest weight was 123 pounds; admission weight was 109 pounds. He felt loss of strength very much.

Physical Examination.—Patient was a pale, poorly developed, poorly nourished boy of 18 years, height 163 cm., weight 42.7 kg. There were small but distinctly palpable nodes on both sides of the neck. Thorax was carinate. There was retraction above and below clavicles, more marked on the left side. The entire left chest showed retraction and marked limitation of expansion. Lungs: Both upper lobes were dull on percussion, the left to the second intercostal space in front and to the angle of the scapula behind; the right was dull only above the clavicle in front and to the spine of the scapula behind. Over these dull areas the breath sounds were bronchial in quality, with many medium sized and fine râles. No excursion of the left base was found, while the maximum excursion of the right base was 2 cm. At the left base there was slight dulness, bronchovesicular breath sounds and many moist râles, front and back. Heart not enlarged nor displaced. There were no murmurs. The rate was quite rapid, but the rhythm was regular. Pulse was rapid and soft. Blood pressure: Systolic 120 mm.; diastolic 80 mm.
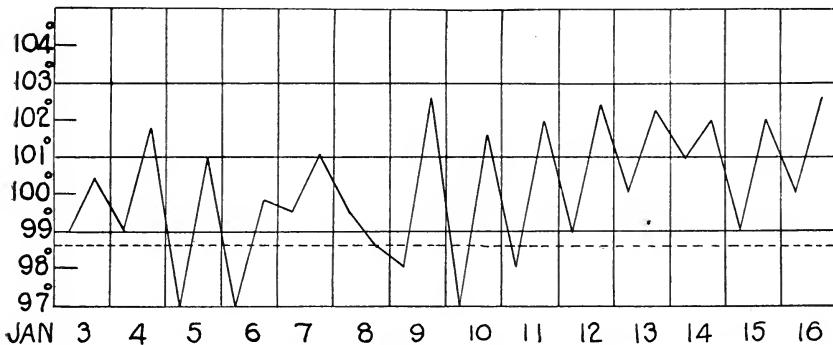
Fig. 5.—Temperature chart of Harry G.

Further examination negative. Urine was normal. Sputum showed numerous tubercle bacilli. Fluoroscopy showed a very diffuse parenchymatous infiltration of both upper lobes, particularly of the left side, with a small antrum beneath the left pole (Dr. J. A. Miller).

One observation was made in the calorimeter January 13. The temperature fell from 39.20 to 38.94 C., pulse 120. The metabolism was 21 per cent. above the average normal, but the conditions were not basal on account of restlessness.

CASE 8.—Joseph D. *Pulmonary tuberculosis, infiltration of both upper lobes and left base.*

History.—A machinist, aged 33 years, was admitted Dec. 3, 1919, complaining of pain in the left side of the chest and cough. His father, mother and one brother died of pneumonia and one uncle died of "lung trouble." In childhood he had dysentery, mumps, whooping cough, "chills and fever." In 1915 he was treated for "lung trouble" in a hospital. He had a bad cough at that time. While under treatment he worked for one year. In April, 1919, he was in Bellevue Hospital on account of pleurisy and cough. Following this he had a chronic cough and occasionally night sweats. He was very short of breath on exertion and had palpitation but no edema. His appetite was good, bowels regular. He urinated three to four times during the night. He had gonorrhea fifteen years ago. His best weight was 135 pounds.

Nov. 25, 1919, while digging a trench, he felt a sudden, sharp pain in the left side of the chest and across the back. He stopped work but did not go to bed. Pain and cough increased daily so that he entered the hospital December 3. At that time the physical findings, confirmed by the roentgen ray, led to a diagnosis of bilateral apical tuberculosis. The temperature range was from 97.4 to 100 F. Leukocytes, 14,000, with polymorphonulcears 65 per cent.; lymphocytes, 23 per cent.; large mononuclears, 10 per cent.; eosinophils, 1 per cent. Hemoglobin, 73 per cent. Urine was normal.

He was allowed to leave the hospital on pass, but did not return. He was readmitted Jan. 14, 1920, with a temperature of 102 F., having had severe chills.

Physical Examination.—A well developed, fairly well nourished man, height 177 cm., weight 59 kg., face flushed, eyes bright, respirations rapid but not labored. Chest: Retraction of both supraclavicular and infraclavicular fossae. Expansion limited most markedly on the right side. Lungs: Both apices were dull from the second intercostal space in front to the spine of the scapula behind and there was dulness at the left base behind. Breath sounds at both apices were tubular, with crepitant and moist râles. In the left chest in front there was a coarse friction rub between the fourth and seventh intercostal spaces. At the left base behind many coarse râles were heard. Heart was not enlarged; rate 80; rhythm regular; no murmurs. Pulse was full and soft, artery not thickened. Further examination was negative.

The patient improved rapidly though he had a moderate, irregular fever for about nine days. January 15 he complained of huskiness of the voice and pain in the larynx on swallowing. Examination showed a thickening of the arytenoids and of the anterior commissure. The cords were thickened and lacked the normal luster but approximated throughout.

Laboratory Examination.—Sputum showed no tubercle bacilli. The roentgen ray showed a patch of peribronchial infiltration in the peripheral portion of the right apex. There was fibrosis of the left apex, emphysema of both lungs, more on the right. There was production of fibrous tissue in the lower lobe of the left lung, but no peribronchial infiltration. Adhesions at the left base.

Diagnosis.—Early second stage tuberculosis, right apex; fibroid tuberculosis, left apex; interstitial inflammation of the left lower lobe; pleural thickening of the right upper lobe; deviation of the heart to the right, axis almost vertical.

The last day of fever was January 16. He was put in the calorimeter on the seventeenth, at which time his basal metabolism was found to be 90 per cent. of the average normal in one hour in which he was very quiet.

Case 9.—Michael C. *Pulmonary tuberculosis with cavitation, laryngeal tuberculosis.*

History.—A furrier, aged 33 years, complained of hoarseness and shortness of breath. He was in perfect health up to January, 1919, when he engaged in a drinking bout with some friends. He sang very loudly and on the following day he was quite hoarse. Soon a cough developed with some expectoration. No medicine gave any relief, his cough and hoarseness grew worse, he began to have night sweats and to lose weight and strength. He remained at work, however, until August, 1919. At this time he became very short of breath and felt great oppression of the chest. His cough was more and more productive, but hemoptysis occurred on only one occasion and then in very small amount. He spent November and December in Colorado, where he improved somewhat. Two weeks before admission he returned to New York. He caught cold and had a recurrence of his worst symptoms. He developed complete aphonia. His best weight was 130 pounds; admission weight was 110 pounds.

Physical Examination.—Fairly well developed but emaciated man, height 179 cm., weight 50 kg., lying flat in bed, breathing rapidly, extremely weak and ill. Laryngeal examination was difficult, but showed marked congestion of epiglottis, arytenoids and vocal cords and laryngeal walls. There were a few enlarged lymph nodes in the neck on both sides. Thorax was well formed,

but there were retractions above and below both clavicles. Expansion was limited on both sides, but more so on the right. Lungs: Both apices dull to percussion, right front dull to the fifth rib and behind to the angle of the scapula. The left apex was dull from the second rib to the middle of the scapula behind. Over the dull areas the breathing was in general broncho-vesicular, with many fine and medium moist râles. Over the third intercostal space in the mid-clavicular line the breathing was amphoric in character. Further examination was negative.
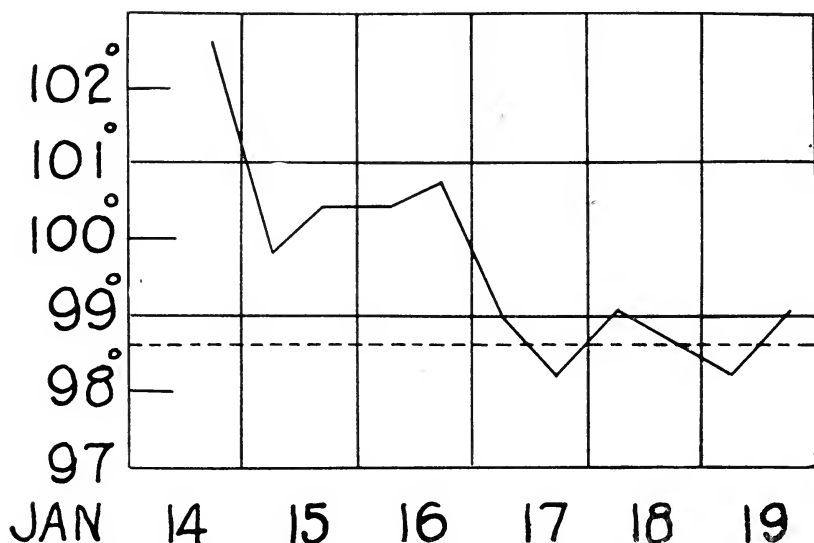
Fig. 6.—Temperature chart of Joseph D.
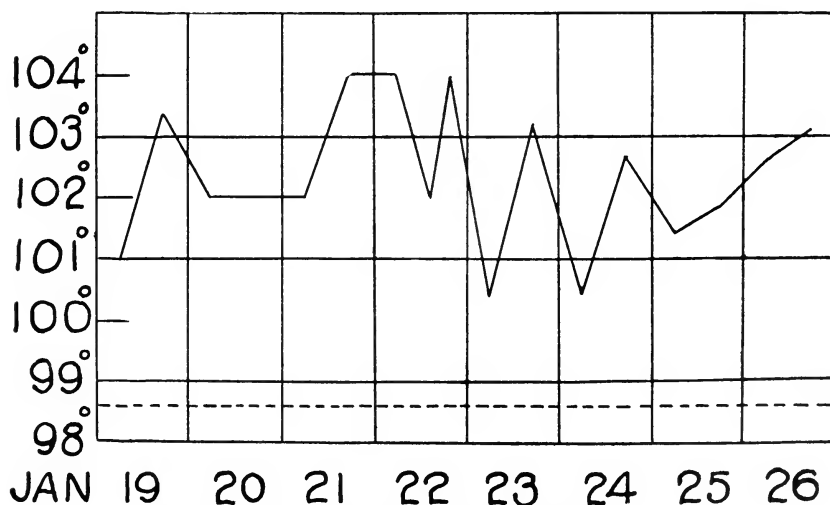
Fig. 7.—Temperature chart of Michael C.

Pulse ranged from 86 to 128 and respirations from 22 to 28. Sputum was full of tubercle bacilli. Urine was normal.

The patient was observed in the calorimeter Jan. 22, 1920. With the rectal temperature falling from 39.8 to 39.2 C. and pulse 120, the metabolism was 31 per cent. the first hour and 24 per cent. the second hour above the average normal; the conditions were not basal as the patient coughed incessantly. The subsequent history is unknown.

Case 10.—Anna H. *Bronchopneumonia; phthisis.*

History.—Sewing machine girl, aged 17 years, was admitted Jan. 25, 1920, complaining of pain in the chest and cough. She had worked two years in the factory, during which time her weight had dropped from 122 pounds to 113 pounds. She was well up to the onset of the present illness, which began Nov. 25, 1919, with a bad cold. The cold did not improve, but she remained at work until Jan. 11, 1920, when her illness became acute, with severe cough and pains in the chest. After remaining in bed for two days she attempted to return to work. She became worse rapidly, coughed constantly and had night sweats. Her weight dropped from 113 to 90 pounds.

Physical Examination.—On admission, January 25, the pharynx was congested, tongue coated, heart normal. Lungs showed no dulness, but numerous, squeaking râles were heard on both sides in back. Temperature, 103 F.; pulse, 100.
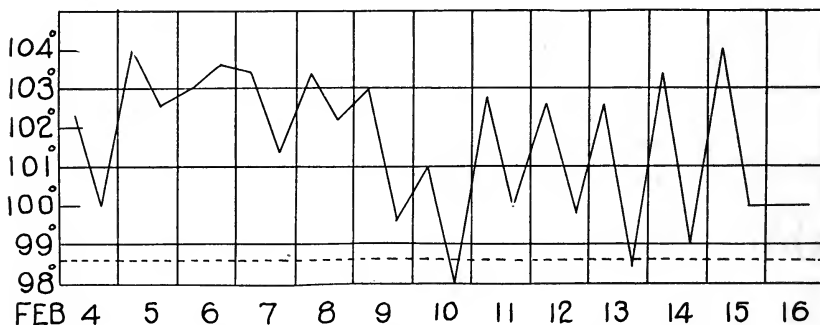
Fig. 8.—Temperature chart of Anna H.

Tentative Diagnosis.—Acute bronchitis.

January 28 numerous tubercle bacilli were found in the sputum. On the following day a note was made: "Thorax symmetrical and well developed. Respiratory excursion is slightly restricted. There are no retractions or bony prominences. There is a widespread process extending through all lobes of both lungs, but most advanced at the bases, characterized by bronchovesicular breathing, and many fine, medium and large moist râles. At both bases posteriorly there is dulness, most marked at the left. At the apex of the heart there is a localized systolic murmur. Over the base of the heart there is a longer, rough murmur heard in systole."

Laboratory Examination.—Urine examinations were all normal. Blood: Feb. 4: Leukocytes, 10,000; polymorphonuclears, 70 per cent.; transitionals, 2 per cent.; lymphocytes, 25 per cent.; eosinophils, 3 per cent. Hemoglobin, 60 per cent.

She was studied in the calorimeter February 5. The temperature rose from 39.38 to 39.64 C.; pulse 132. The metabolism was 21 per cent. above the average normal, but was not basal, as the patient was coughing throughout the observation.

February 7 the physical examination was as follows: "A normally developed girl of 17, past puberty, very emaciated and pale, height 165 cm., weight 41 kg. There is a bright flush over the left malar region; eyes are bright; breathing very rapid but not labored. Thorax shows limitation of expansion of the left

side. There are retractions above the clavicles, and on the left side in the first and second interspaces and at the left base and axilla. Lungs are dull at both apices, and the left lung is dull throughout. The right base is resonant below the angle of the scapula. Over the dull area there is an increase in vocal and tactile fremitus, tubular breathing at the apices and bronchovesicular breathing at the left base. Over the whole chest fine, medium and coarse moist râles are heard. Heart is normal. Pulse rapid, 120, regular, and of very low tension. Abdomen is somewhat distended, but otherwise normal." Further examination was negative.

February 20 the signs of consolidation were intensified. Numerous crackling râles and in many places creaking friction rubs were heard.

The patient died two days later. A necropsy was not permitted.

CASE 11.—John H. *Pulmonary tuberculosis.*

History.—A chauffeur, aged 25 years, was admitted complaining of pain in the chest, headache and chills. He was well and strong up to the time of his enlistment in the British Army, Tank Service, in 1916. He served nine months at the front and remained well until he was gassed with chlorin. He was sick for three or four months with cough and afternoon fever, but was finally returned to duty. He remained well and was discharged physically fit. He was able to do all sorts of work up to the end of November, 1919, when he
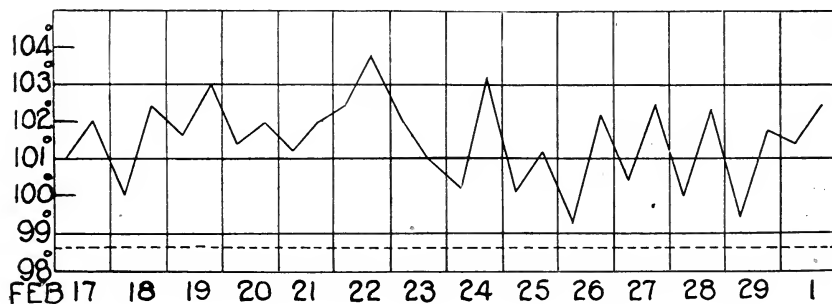
Fig. 9.—Temperature chart of John H.

was taken sick with pneumonia and treated in the Metropolitan Hospital for four weeks. He had been out of the hospital only three weeks when he was again taken sick and admitted to Bellevue Jan. 24, 1920. Three days before admission patient had a severe cough and soreness in the chest. He went to bed and stayed there until the following day. A doctor gave him some whisky. He took it and the next day was admitted in an intoxicated condition. Later he said his best weight was 142 pounds and that he had maintained this up to November. Present weight, 100 pounds.

Physical Examination.—Height, 175 cm., weight 45 kg. Well developed, pale, emaciated young man. Lips somewhat cyanotic and parched. Chest: Well formed with deep supraclavicular fossae. Expansion was fairly good, but more limited on the right side. Lungs: Left apex was dull from the second rib in front to midscapula behind, with bronchovesicular breathing and many fine râles. Left base was resonant except in midaxilla, where there was slight dulness and a creaking rub was heard. The right lung was dull throughout, most marked at the apex, where the breath sounds were tubular and accompanied by fine râles. At the right base the breathing was bronchovesicular, with many medium and fine râles. Heart was normal in size and position; no murmurs. Rhythm was regular. Pulse was soft and rapid. Blood pressure: Systolic 100; diastolic 60. Further examination was negative.

Laboratory Examination.—Sputum contained many tubercle bacilli. Urine examinations were normal throughout. Blood: Leukocyte counts, January 26, 10,500; February 6, 13,600; polymorphonuclears, 64 per cent.; transitionals, 18 per cent.; lymphocytes, 4 per cent.; large mononuclears, 13 per cent.; eosinophils, 1 per cent. Roentgenogram of chest, February 9, showed diminished illumination over the upper halves of both pulmonic fields. There was considerable increase in the size, number and density of the pulmonic markings throughout this area. These markings were confluent. There was considerable increase in density of both hilus shadows. The costophrenic sinuses were clear. The diaphragmatic outlines were normal. The heart shadow was slightly displaced to the left. Infiltration of upper halves of both lungs.

Diagnosis.—Tuberculosis.

He was studied in the calorimeter February 10. With a normal temperature his basal metabolism was 15 per cent. above the average normal. February 12, the specific dynamic effect of a meat meal was studied (Fig. 15). This meal

TABLE 5.—DIET CHART AND NITROGEN BALANCE IN CASE 11

| Name and Date | Food | | | Food N, Gm. | Urine N, Gm. | Feces N, Gm. | Excreta N, Gm. | N Balance, Gm. | Body Weight, Kg. |
	Total Calories	Carbohydrate, Gm.	Fat, Gm.						
John H.									
4/17/20	1,650	147	83	10.7	9.0	1.1	10.1	+0.6	44.6
4/18/20	1,977	185	92	14.2	....	1.4			
4/19/20	1,830	194	73	13.8	9.0	1.4	11.4	+2.4	44.3
4/20/20	.....	...	...	....	6.8	...	....	.....	44.7
4/21/20	.....	..	...	....	10.8				
4/23/20	1,890	156	95	14.5	....	1.5	....	.....	43.8
4/27/20	1,848	152	93	14.1	14.5	1.4	15.9	—1.8	
4/28/20	1,848	152	93	14.1	17.6	1.4	19.0	—4.9	44.0
4/29/20	1,848	152	93	14.1	13.7	1.4	15.1	—1.0	44.2
4/30/20	1,964	173	95	14.4	12.3	1.4	13.7	—0.7	43.9
5/ 1/20	1,964	173	95	14.4	11.6	1.4	13.0	+1.4	43.8
5/ 2/20	2,055	180	100	15.0	11.6	1.5	13.1	+1.9	
5/ 3/20	2,123	185	104	15.7	13.9	1.6	15.5	+0.2	44.3
5/ 4/20	1,734	169	92	7.1	7.6	2.1*	9.8	—2.6	
5/ 5/20	1,739	169	93	7.1	8.8	2.1*	10.9	—3.8	44.7
5/ 6/20	1,739	169	93	7.1	5.7	2.1*	7.8	—0.7	44.7
5/ 7/20	1,737	169	92	7.1	6.4	2.1*	8.5	—1.4	
5/ 8/20	1,737	169	92	7.1	3.8	2.1*	6.9	+0.2	44.7
5/ 9/20	1,737	169	92	7.1	5.6	2.1*	7.7	—0.6	
5/10/20	1,737	169	92	7.1	5.4	2.1*	7.5	—0.4	44.9
5/11/20	2,975	188	121	3.2	5.4	1.0	6.4	—3.2	44.8
5/12/20	2,955	183	121	3.3	4.6	1.0	5.6	—2.3	44.5
5/13/20	1,914	181	118	3.0	3.7	1.0	4.7	—1.7	44.0
5/14/20	1,914	181	118	3.0	3.1	1.0	4.1	—1.1	44.3
5/15/20	1,915	181	118	3.0	....	...	....	.....	44.2

* Analysis made.   Remaining fecal nitrogen estimated.

consisted of 350 gm. of lean beef and 10 gm. butter (protein 70 gm., fat 28 gm.). From a basal heat production of 69.3 calories per hour, his metabolism rose in successive hours after the meal to 77.0, 82.4 and 86.8 calories per hour, respectively. This corresponds closely with the results obtained with normal subjects.

Considerable improvement in the patient's condition occurred, his appetite was better. He still had considerable pain in the left chest.

March 1 his metabolism was 17 per cent. above the average normal, temperature betwen 38.68 and 38.71 C., very quiet.

During the month of March marked improvement continued. The temperature range gradually became smaller and lower. His cough almost ceased. His appetite was good and during this time he was given the ordinary soft, special diet of the hospital, not measured. The total caloric value of this diet is not high. He remained at the same weight, 100 pounds, with very slight variations.

His basal metabolism was again determined April 14; rectal temperature from 37.8 to 37.4 C. His metabolism was 5 per cent. above the average normal. From this his daily basal heat production was estimated at 1,512 calories. This was done as a preliminary to complete dietary control in the metabolism ward. The temperature and graphic record of this study are given in Figure 18. The observed data are given in Table 5. The stools for the different periods were marked off with carmine and saved for analysis, the total nitrogen for the period was determined, and the daily average added to the urine nitrogen figure. The study was made to determine the minimum level at which nitrogen balance could be attained and the minimum to which the protein metabolism could be reduced as a means of estimating the toxic destruction of protein.

CASE 12.—William H. *Pulmonary tuberculosis, tuberculosis of hip joint.*

History.—A laborer, aged 31 years, was admitted in February, 1920, complaining of pain in the chest, cough, loss of weight and weakness. At the age of 2 he had whooping cough and later measles. When 3 years old he had hip disease, for which he was treated at the Postgraduate Hospital. He wore a brace until the age of 13. During this period his health was good. His growth was normal. He had always done hard manual labor outdoors until shortly before the present illness. Late in the fall of 1919 he worked in a factory
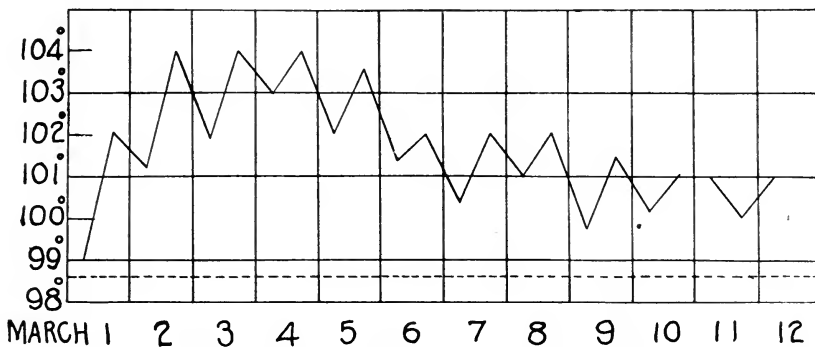
Fig. 10.—Temperature chart of Wm. H.

where he was confined in a dusty room. He felt wretched during his stay in this position and gave it up. He then worked on the city streets shoveling snow. February 7 he became very wet and was exposed all day. He felt a sudden, sharp pain in the left chest and back. In the Bellevue Dispensary tubercle bacilli were found in the sputum and, therefore, he was admitted to the hospital. During the week prior to admission he had night sweats, severe cough, with abundant sputum in which no blood was noted. His best weight was 135 pounds, but just before the onset of illness it was 130 pounds. Weight while in the hospital was 110 pounds.

Physical Examination.—Height 165 cm., weight 49.7 kg. Patient was a fairly well nourished young man of medium size who looked acutely ill. Thorax: Slight asymmetry due to a scoliosis. Respiratory movements fairly free and symmetrical. There were no retractions. Lungs: Apices were dull on both sides above and just below the clavicles. Behind, the dulness, which was most marked at the extreme apex, shaded into normal resonance about the level of the sixth dorsal spine. Over the apices the breath sounds were bronchovesicular, with many fine râles. Between the scapula many coarse moist râles and sibilants were heard. Elsewhere the breath sounds were normal. Heart: Of normal size and position. No adventitious sounds were heard. The rate was rapid, rhythm regular. Pulse rapid and soft. Blood pressure: Systolic, 105 mm.; diastolic, 85 mm. There was ankylosis of the left hip, with

complete limitation of motion. The muscles of the left thigh and calf were atrophied. The left leg was two inches shorter than the right. There were no other abnormalities.

Laboratory Examination.—Sputum contained many tubercle bacilli. Urine examinations were normal throughout. Blood: Leukocyte count, March 3, 10,400; hemoglobin, 90 per cent. March 8: Wassermann reaction negative. Roentgen-ray report showed pulmonic fields of equal size. There was diminution of illumination over the upper half of the left pulmonic field. The apices were clear. There was considerable increase in the hilum shadows, with calcific foci on the right. The pulmonic markings were increased in size, number and density over the upper half of the left pulmonic field, with agglutination. Over the right pulmonic field there was increase in the size, number and density of the pulmonic markings, with confluence. There was an irregularity in the outline of the right diaphragm. The costophrenic sinuses were clear. The heart was large, generally rounded in outline and median in position.

March 24: Vital capacity equaled 2,795 c.c. The normal for the present surface area, according to the calculations of West, is $1.53 \times 2,500 = 3,825$ c.c., but the normal surface area for health is 1.66 square meters, hence the normal vital capacity would be 4,150 c.c.

March 2 the metabolism was 18 per cent. above the average normal when his temperature was 38.58 C. and the patient was very quiet. At the same temperature in the next hour the heat production was raised 5 per cent. more by coughing.

March 10 the basal metabolism was 9 per cent. above the average normal when the rectal temperature was 38.0 C.

The specific dynamic action of a protein meal was studied. The meal consisted of 350 gm. meat with 10 gm. butter (protein 70 gm., fat 28 gm.). From a basal heat production of 65.6 calories per hour, the metabolism rose after the meal to 68.7, 73.9 and 86.1 calories per hour in successive hours. This corresponds closely with the behavior of the normals studied (Fig. 15).

CASE 13.—John S. *Pulmonary tuberculosis, mitral stenosis, and regurgitation, compensated.*

History.—A machinist, aged 28 years, was admitted complaining of a feeling of fatigue and of swelling of the feet and ankles. He had no illness in childhood except occasional sore throat. At the age of 20 he had mumps. In 1913 he had typhoid fever. In 1919 he had two attacks of acute rheumatic fever. He had gonorrhea three times. He was in quite good health until the spring of 1919, when he had a severe cold, which persisted. He had a dry, hacking cough, which grew much worse in the course of several weeks. He lost appetite and began to have fever in the afternoon, with great weakness and prostration. He remained at work even when his temperature was high. Sputum examination by the board of health showed tubercle bacilli. At this time his afternoon temperature was 103 F. His weight dropped from 160 to 154 pounds. He was sent to a hospital for tuberculosis and later transferred to Otisville. He improved, became afebrile, and regained weight up to 160 pounds. While there he developed acute rheumatic fever after lying on the wet grass when overheated from work. He soon recovered, but had another attack in August, 1919. Following the second attack he had edema of the ankles while at work. For the past year he had to urinate three or four times during each night. Maximum weight in 1913 was 168 pounds; weight before illness in 1919 was 160 pounds; weight while in hospital, 148 pounds.

Feb. 5, 1920, his feet began to swell and he felt very tired. This continued, causing him to stop work February 10. He was admitted to Bellevue February 12, with a fever of 104 F., falling to normal in the course of forty-eight hours, and then fluctuating between 99 and 100 F. He had a mild cardiac decompensation from which he rapidly recovered, though he continued to have fever from a reactivation of his tuberculosis.

Physical Examination.—Patient was a well developed man, 191 cm. in height, weighing 62.3 kg. Thorax well formed, supraclavicular fossae deep, but

with greater retraction on the left. There was limitation of expansion of the left chest. Lungs were dull on percussion of both upper lobes, the left upper from the fourth rib in front to the angle of the scapula behind, the right from the third rib in front to the midscapula. Expiration was prolonged and high pitched, with many medium and fine râles. Heart: Apex impulse in the fifth intercostal space was 12 cm. to the left of midline. Dulness extended to the left 13 cm. in the fifth space and to the right 6 cm. in the fourth intercostal space. There was a suggestion of a thrill over the precordium. There was a presystolic murmur of rough, crescendo quality at the apex, and also a systolic murmur heard at the apex, in the axilla and to the right of the sternum in the fourth space. The second pulmonic sound was accentuated. The rate was
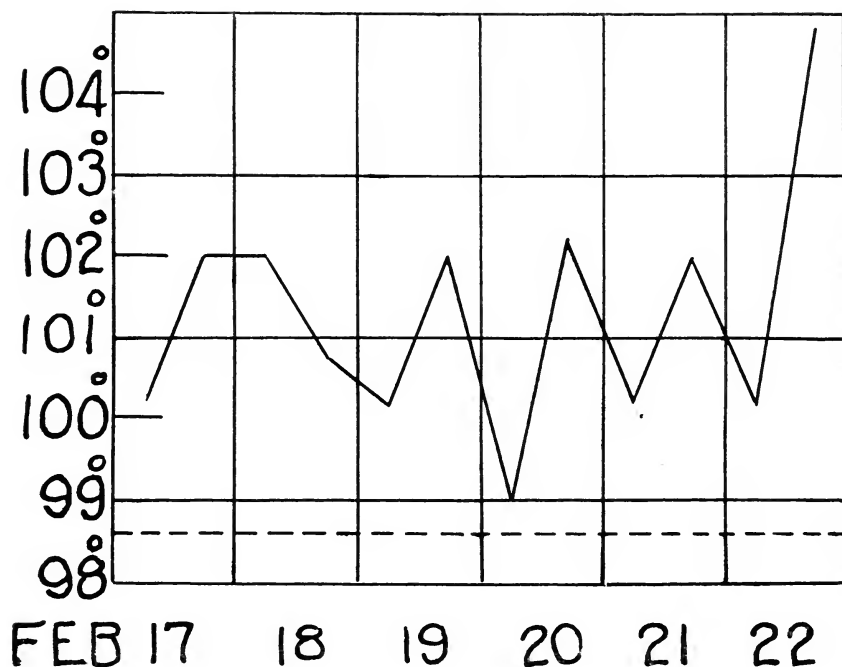
Fig. 11.—Temperature chart of John S.

120, rhythm regular. Pulse was dicrotic. Blood pressure: Systolic, 105 mm.; diastolic, 60 mm. Liver was not felt. Further examination was negative.

Laboratory Examination.—Sputum contained many tubercle bacilli. Blood: Leukocyte count on admission was 14,200, of which 84 per cent. were polymorphonuclears, 4.5 per cent. large mononuclears, 1.5 per cent. transitionals, 9.5 per cent. lymphocytes. Red cell count was 4,152,000. Hemoglobin, 75 per cent. Urine examination was negative.

He was studied in the calorimeter February 17, at which time his basal metabolism was found to be 14 per cent. above the average normal, with temperature falling between 37.8 and 37.4 C. On a second occasion the observation was unsuccessful because he was eliminating water from the skin and lungs at the rate of about 72 gm. per hour, which surpassed the capacity for ventilation of the calorimeter.

CASE 14.—George M. *Pulmonary tuberculosis, with cavitation.*

History.—A machinist's helper, aged 31 years, was admitted March 15, 1920, complaining of chills, fever and night sweats and severe cough. In childhood he had whooping cough and measles at the age of 9 years. He was in perfect health until he went to India in 1917 in the transport service of the Mesopotamia campaign. While there he had "sand fly fever," for which he was treated with quinin. He also had dysentery which became chronic. Each winter following 1914 he had colds and persistent cough, nevertheless remaining in fairly good health. His appetite was habitually poor. He had a soft chancre in 1911 and later had gonorrhea also. He has had no secondary manifestations of syphilis. His maximum weight was 137 pounds.

In the winter of 1919-1920 the patient had his usual winter cough, but it was much more severe than usual. It kept him awake at night. He became very weak and "run down." Sputum was never bloody. About February 15 he began to feel chilly in the afternoon and at night he had severe sweats.
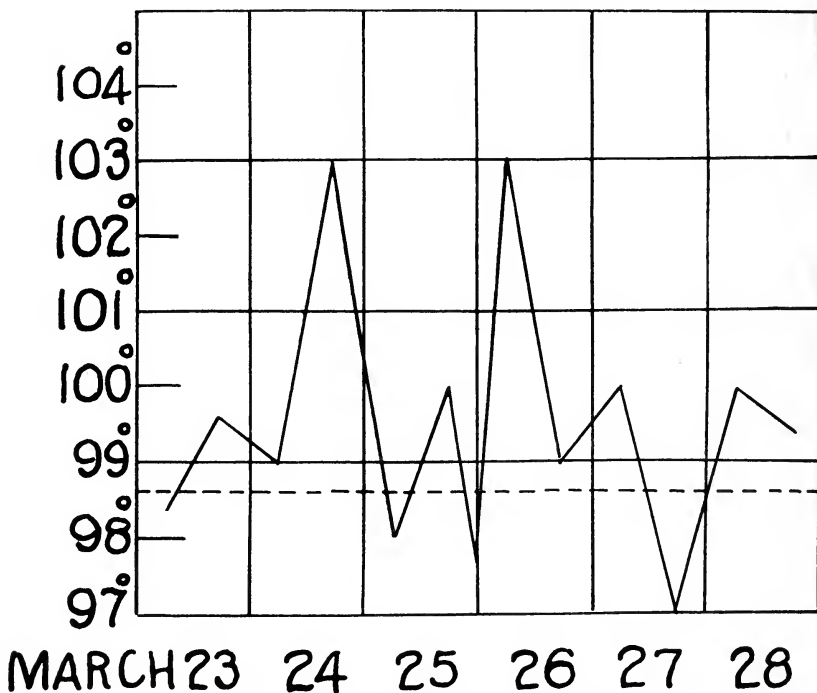
Fig. 12.—Temperature chart of George M.

His cough became worse and the expectoration blood tinged. He had had much substernal and precordial pain, aggravated by coughing. Vomiting was sometimes induced by the severity of the cough.

Physical Examination.—The patient was a small, thin man, 165 cm. tall, weighing 49.1 kg. Thorax of normal shape, but with marked supraclavicular retractions. Respiratory excursions were symmetrical and apparently not limited. Lungs: Both apices quite dull on percussion from the third rib in front to the angles of the scapulae behind. Over the dull areas there was increased fremitus and whispered voice transmission, bronchial breathing and many fine râles. At the right apex the breathing approached amphoric in quality, especially at the extreme upper part of the right axilla. The bases were slightly dull posteriorly and the excursion of neither base exceeded one finger's breadth.

There was bronchovesicular breathing at the right base and a few coarse râles were heard at both bases. Heart not enlarged nor displaced; rate 100; rhythm regular. Blood pressure: Systolic, 85 mm. There were a few palpable nodes in both inguinal regions. Moderate clubbing of fingers. Further findings were negative.

Laboratory Examination.—Sputum examination showed many tubercle bacilli. Urine normal. Blood: Leukocyte count (March 17), 11,400, of which 60 per cent. were polymorphonuclears, 29 per cent. lymphocytes, 9 per cent. large mononuclears, 1 per cent. transitionals, 1 per cent. eosinophils. March 26: Leukocytes, 11,000; polymorphonuclears, 73 per cent.; lymphocytes, 17 per cent.; large mononuclears, 10 per cent.

Vital capacity, average six trials, 2,523 c.c., which is 61 per cent. of the normal, as calculated by the method of West from the surface area.

This patient was observed in the calorimeter March 24 while the temperature was falling rapidly from 39.56 to 38.72 C., with sweating. The metabolism in the first hour was 34 per cent. above the average normal and during the second it was 27 per cent. above. March 26 another observation was made while the temperature fell from 39.23 to 38.17 C., the metabolism being 29 per cent. above the average normal. The percentage of heat lost through vaporization was from 32 to 35 per cent. of the total heat eliminated. This latter observation is graphically represented in Figure 14. The conditions were not basal in either case, due to restlessness.

Case 15.—Joseph R. *Pulmonary tuberculosis with cavitation; chronic nephritis with hypertension.*

History.—A printer, aged 36 years, was admitted May 3, 1920, complaining of "kidney trouble." While his health, in general, had always been good, he had had for a long time a slight, hacking cough, not productive, believed to be due to excessive smoking. He had been a heavy beer drinker. For many years he had urinated once during the night. His maximum weight was 180 pounds. In 1918 he lost weight rapidly to 161 pounds. His weight remained at 160 until six weeks before admission, when he again began to lose. Weight while in hospital was 134 pounds. About one week before admission he noticed swelling of the ankles and legs, extending within the next few days to the trunk and face. He felt nauseated and had some attacks of vomiting. He then began to urinate five or six times a night. He had not been conscious of fever and had had no night sweats. His cough had become productive, but there had been no hemoptysis.

Physical Examination on Admission.—Height, 175 cm.; weight, 61.13 kg. Patient was a well developed but rather poorly nourished man; lips somewhat cyanotic. He showed slight dyspnea, but sat up in bed reading comfortably. There was a slight venous pulsation in the neck. Chest was of normal shape and size. There were moderate retractions of the upper left side, seen chiefly in the second and third intercostal spaces. Lungs: Marked diminution of resonance over the whole left chest, with hyperresonance of the right. The upper left chest anteriorly was almost flat and fremitus was increased. Over this area the breath sounds were somewhat amphoric in quality. Elsewhere on the left the expiration was prolonged and high pitched. Heart: There was a general heaving of the precordium. The apex impulse was of maximum intensity in the fifth intercostal space 12 cm. to the left of the midline. The cardiac dulness extended from the right sternal margin to 14 cm. to the left in the fifth intercostal space. Rhythm was regular. There were no murmurs. There was slight accentuation of the aortic second sound. Blood pressure: Systolic, 160 mm.; diastolic, 120 mm. Arteries not thickened. Abdomen was somewhat distended and tender in the right upper quadrant. Liver was felt three fingers' breadth below the costal margin. Hands were somewhat cyanotic and puffy, but did not pit. There was some edema of both lower extremities and under the sacrum.

Laboratory Examination.—The urine showed a low specific gravity (1.010), considerable albumin, no sugar, many hyalin and granular casts, many red blood cells and many clumped leukocytes. Blood: May 4, leukocytes, 10,000; hemoglobin, 70 per cent.; May 6: nonprotein nitrogen, 39.5 mg. per hundred c.c.; creatinin, 1.7 mg. per hundred c.c. May 5 the sputum contained many tubercle bacilli.

The patient improved rapidly. May 12 the dyspnea was almost gone; edema very slight. The roentgen ray showed pulmonic fields of unequal size, the right being larger than the left. There was marked diminution of the illumination throughout the entire left pulmonic field, and the middle third of the right. Costophrenic spaces were clear. There was increase in size and density of the right hilum shadow. There was increase in size, number and density of the left pulmonic and also of the middle third of the right field, markings agglutinated throughout. Large cavity at the left apex. Diaphragm shadow normal. Heart enlarged, distorted in appearance, with adhesions. Fibrosis, infiltration and cavitation of the left lung, tuberculosis.

May 24 there was no edema or dyspnea. Blood pressure: Systolic, 128 mm.; diastolic, 110 mm. Fundus of each eye normal. Comfortable.

May 25 he was studied in the calorimeter. Rectal temperature 36.7 C. His heat production was 70.7 calories per hour, or 40.5 calories per square meter per hour, being 3 per cent. above the average normal. He was then studied in the metabolism ward. The diet given is shown in Table 6 and graphically in Figure 19.

May 26 the nonprotein nitrogen content of the blood was 26 mg. per hundred c.c.

June 1, 1920, a cystoscopy was done. The cystoscope passed easily into the bladder and some clear urine was obtained. Bladder capacity normal. Bladder neck and fundus normal, but many trabeculations were seen on the posterior bladder wall. Mucosa normal. Both ureteral orifices were normal. Specimens were obtained from both sides, but no further report was made.

TABLE 6.—Diet Chart and Nitrogen Balance in Case 15

Name and Date	Total Calories	Carbohydrate, Gm.	Fat, Gm.	Food N, Gm.	Urine N, Gm.	Excreta N,* Gm.	N Balance, Gm.	Body Wt., Kg.	Urine Vol., C.c.	Water Intake, C.c.	NaCl Intake, Gm.	Urine NaCl Gm.
Joseph R.												
5/15/20	1,678	165	83	9.1	9.5	10.5	—1.4	64.0	2,155	1,900	7.61	
5/16/20	1,886	183	92	10.8	10.6	11.6	—0.8	....	2,080	1,990	7.61	
5/17/20	1,823	189	85	10.0	10.7	11.7	—1.7	62.5	2,080	2,000	7.99	8.48
5/18/20	1,992	229	85	10.2	8.0	9.0	+1.2	61.8	2,210	2,224	7.45	9.57
5/19/20	2,261	277	94	10.0	8.2	9.2	+0.8	....	1,630	2,000	7.26	6.15
5/20/20	2,002	250	78	9.9	8.1	9.1	+0.8	....	1,740	2,000	7.23	6.80
5/21/20	1,914	220	86	8.3	7.6	8.6	—0.3	62.0	2,135	2,000	7.40	7.29
5/22/20	2,248	238	123	4.9	7.6	8.6	—3.7	....	2,135	2,000	7.66	7.29
5/23/20	1,998	248	93	4.6	5.6	6.6	—2.0	....	2,155	2,000	6.85	8.32
5/24/20	2,085	269	93	4.8	5.7	6.7	—1.9	62.3	2,350	2,000	6.94	9.13
5/25/20	1,772	251	67	4.6	5.1	6.1	—1.5	61.3	1,930	2,000	6.87	8.06
5/26/20	2,370	302	113	3.4	5.1	6.1	—2.7	....	2,580	2,000	6.58	11.15
5/27/20	2,510	332	114	3.3	4.3	5.3	—2.0	60.8	2,520	2,000	6.33	10.96
5/28/20	2,493	327	115	3.3	2.5	3.5	—0.2	60.4	1,480	2,000	6.54	5.50
5/29/20	2,555	342	115	3.4	4.3	5.3	—1.9	....	2,380	2,000	6.55	9.26
5/30/20	2,493	327	115	3.3	3.9	4.9	—1.6	59.4	2,455	2,000	6.54	8.59

* Estimated.

Comment.—The tendency to retain nitrogen in the blood in this case is negligible. The nonprotein nitrogen of the blood before beginning the diet was 39.5 mg. per hundred c.c., while on May 20, before the food nitrogen was reduced, the nonprotein nitrogen was only 26 mg. per hundred c.c. The explanation of the loss in weight becomes apparent at once on examination of the intake and output of salt and water. The weight declined as an excess of salt and water were eliminated, and the edema disappeared.

DISCUSSION OF RESULTS

The results of the observations made in the calorimeter are shown in Table 7. The respiratory quotients are all within normal limits. The average quotient for fasting [25] observations is 0.79, so that there is no evidence of a qualitative change in the combustions as far as the respiratory quotients are concerned.

Regarding quantitative changes in the metabolism, the data are presented from two points of view in Table 8. It is customary to compare the observed heat production of a patient with the theoretical heat production of a normal man of the same surface area. The percentage variation from the average normal metabolism is shown. It will be observed that in only ten of the fifteen cases were there observations which were considered basal; that is, in the condition of complete rest in the fasting state. The conception of the basal metabolism on which this was based implies the minimal metabolism. If the patient had fever at the time of observation it was considered basal only if the temperature was approximately at the lowest part of the diurnal variation. In the case of Robert W., the patient was very quiet at a temperature of about 40 C. This was not considered basal because the temperature was near the peak of the diurnal curve. In the first hour of the observation on Trellis H. the patient was also very quiet at a similar temperature. If one considers these as basal periods then it may be said that the basal metabolism at 40 C. is 28 or 29 per cent. above the average normal. In the ten remaining cases the basal metabolism ranges from 3 per cent. below to 15 per cent. above the average normal. Barbour's three cases lie within this range, so that it appears that the basal metabolism, as conceived above, is but very slightly elevated above that of normal men of the same sur·face area.

It should be remembered, however, that in losing weight the surface area of the patient has diminished. As far as each individual patient is concerned, the normal metabolism is the metabolism in health. Comparison of the present with the probable normal metabolism has been made and is also shown in Table 8, for each case in which the previous weight of the patient was known. It will be observed that in all cases except one, John S., the average hourly basal heat production observed is equal to or less than the estimated calories per hour for the same patient in health. In the case of John S. the increase is slight.

25. Not strictly fasting; small standard breakfast, previously referred to,[18] was given. The effect of this may be considered negligible.

TABLE 7.—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period, Time	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
Chas. G. 5/8/17 52.2 Kg. 1.57 Sq. M.	Prelim.	12:26	....	....	....	....	....	....	....
	1	1:26	22.2	21.0	0.77	30.5	0.30	....	62.2
	2	2:26	22.6	21.0	0.78	30.6	0.30	....	65.7
	Aver.	....	....	....	....	....	....	69.7	....
Chas. G. 5/11/17 52.7 Kg. 1.57 Sq. M.	Prelim.	12:10	....	....	....	....	....	....	....
	1	1:10	23.0	20.2	0.83	28.4	0.33	....	66.3
	2	2:10	23.2	21.7	0.78	38.0	0.33	....	77.2
	Aver.	....	....	....	....	....	....	69.8	....
Chas. G. 5/14/17 52.4 Kg. 1.57 Sq. M.	Prelim.	11:58	....	....	....	....	....	....	....
	1	12:58	22.5	20.2	0.81	47.7	0.31	....	73.1
	2	1:58	23.0	20.4	0.82	39.7	0.31	....	70.0
	3	2:58	22.9	21.3	0.78	42.7	0.31	....	73.5
	4	3:35	13.8	12.7	....	....	....	....	....
	Aver.	....	....	....	....	....	....	68.8	....
Trellis H. 5/9/17 51.7 Kg. 1.57 Sq. M.	Prelim.	11:47	....	....	....	....	....	....	....
	1	12:47	29.7	26.6	0.81	40.1	0.44	98.0	78.4
	2	1:47	26.4	24.2	0.79	33.5	0.44	80.2	74.8
	Aver.	....	....	....	....	....	....	....	....
Robert W. 5/25/17 53.4 Kg. 1.57 Sq. M.	Prelim.	11:18	....	....	....	....	....	....	....
	1	12:18	26.3	23.7	0.81	36.5	0.57	....	72.1
	2	1:18	25.6	25.3	0.74	42.1	0.57	....	73.3
	3	2:18	25.2	23.1	0.80	49.4	0.57	....	93.5
	Aver.	....	....	....	....	....	....	78.6	....
Geo. P. 5/24/17 58.5 Kg. 1.70 Sq. M.	Prelim.	12:07	....	....	....	....	....	....	....
	1	1:07	23.8	21.8	0.79	32.3	0.27	72.7	66.0
	2	2:10*	25.9	23.4	0.80	32.8	0.27	78.3	69.7
	Aver.	....	....	....	....	....	....	....	....
Spencer C. 12/10/19 44.3 Kg. 1.48 Sq. M.	Prelim.	11:41	....	....	....	....	....	....	....
	1	12:41	22.6	18.4	0.89	28.1	....	62.8	54.8
	2	1:41	23.1	19.1	0.88	30.4	....	65.0	58.5
	Aver.	....	....	....	....	....	....	....	....
Edith B. 12/17/19 44.6 Kg. 1.53 Sq. M.	Prelim.	12:47	....	....	....	....	....	....	....
	1	1:47	19.5	17.3	0.82	21.9	....	57.9	49.1
	2	2:47	19.8	18.0	0.80	21.6	....	60.2	47.3
	Aver.	....	....	....	....	....	....	....	....
Edith B. 12/19/19 45.5 Kg. 1.53 Sq. M.	Prelim.	8:50 p.m.	....	....	....	....	....	....	....
	1	9:50	19.6	19.1	0.75	31.6	....	62.8	61.2
	2	10:50	23.9	21.2	0.82	31.1	....	71.2	60.5
	3	11:50	23.2	21.6	0.78	34.6	....	71.7	71.0
	Aver.	....	....	....	....	....	....	....	....
Edith B. 1/6/20 44.0 Kg. 1.53 Sq. M.	Prelim.	2:42 p.m.	....	....	....	....	....	....	....
	1	3:42	22.9	21.0	0.79	27.0	0.07	70.2	59.8
	2	4:42	22.2	20.6	0.78	27.9	0.07	68.9	63.7
	3	5:42	22.6	21.0	0.78	31.0	0.07	70.1	69.1
	Aver.	....	....	....	....	....	....	....	....
Harry G. 1/13/20 42.8 Kg. 1.40 Sq. M.	Prelim.	12:38	....	....	....	....	....	....	....
	1	1:38	23.6	21.5	0.80	39.4	..	71.8	78.2
	2	2:38	24.1	22.6	0.77	38.1	....	75.0	71.5
	Aver.	....	....	....	....	....	....	....	....
Joseph D. 1/17/20 59.0 Kg. 1.74 Sq. M.	Prelim.	12:12	....	....	....	....	....	....	....
	1	1:12	20.5	17.9	0.83	26.0	0.17	60.4	58.5
	2	2:12	21.8	21.0	0.76	29.8	0.17	69.3	67.9
	Aver.	....	....	....	....	....	....	....	....
Michael C. 1/22/20 50.0 Kg. 1.62 Sq. M.	Prelim.	11:50	....	....	....	....	....	....	....
	1	12:50	26.5	25.2	0.76	41.5	0.05	83.8	82.3
	2	1:50	25.7	23.6	0.79	42.5	0.05	79.1	81.6
	Aver.	....	....	....	....	....	....	....	....

—Calorimetric Data

Direct Calorimetry Rectal Temp., Cal.	Rectal Temp., C.	Average Pulse	Work Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohydrate	Per Kg.	Per Sq. M. Linear	
....	37.8	...	....	....	..	..	..	....	....	Basal
64.4	37.9	...	4.0							
67.0	37.9	· ...	6.5							
....	....	116	....	0.77	11	70	19	1.34	44.4	
....	38.6	...	....	....	..	..	..	....	....	Falling temperature
57.2	38.4	...	11.0							
68.6	38.2	...	18.0							
....	....	129	....	0.80	13	59	28	1.33	44.5	
....	38.1	...	....	....	..	..	..	....	....	Basal
60.4	37.8	...	2.5							
73.0	37.9	...	7.5							
70.8	37.8	...	8.0							
....	....	118	....	0.80	12	60	29	1.31	43.8	
....	39.7	...	....	....	..	..	..	....	....	Rising temperature
93.1	40.1	...	18.5	0.81	12	56	32	1.90	62.4	
78.8	40.2	...	....	0.80	15	59	26	1.55	51.1	
....	....	90								
....	40.1	...	....	....	..	..	..	....	....	High temperature, very quiet
65.9	40.0	...	2.5							
68.2	39.6	...	4.5							
80.5	39.4	...	3.0							
....	....	104	....	0.73	19	73	8	1.47	50.1	
....	37.4	...	....	....	..	..	..	....	....	(* 63 min.) Basal; very quiet; work adder broken
75.4	37.6	...	....	0.79	10	64	26			
76.6	37.8	...	....	0.80	10	60	30			
....	....	70	....	....	..	..	..	1.26	43.3	
....	36.6	...	....	....	..	..	..	....	....	Basal
57.8	36.6	...	24.2	....	..	..	..	1.42	42.4	
57.0	36.6	...	1.3	....	..	..	..	1.47	43.9	
....	....	93								
....	37.3	...	....	....	..	..	..	....	....	Basal
67.0	37.8	...	23.0	....	..	..	..	1.30	37.8	
67.0	38.3	...	23.0	....	..	..	..	1.35	39.3	
....	....	116								
....	39.5	...	....	....	..	..	..	....	....	High fever, restless in last hour, quiet in first hour
71.4	39.8	...	25.0	....	..	..	..	1.38	41.0	
65.5	39.9	...	21.0	....	..	..	..	1.57	46.5	
70.0	39.6	...	58.7	....	..	..	..	1.58	46.8	
....	....	125								
....	39.9	...	....	....	..	..	..	....	....	High temperature, coughing
68.5	40.1	...	40.0	0.79	2	68	30	1.64	47.1	
75.0	40.4	...	27.0	0.78	2	73	25	1.56	45.0	
53.1	40.0	...	33.0	0.78	2	72	26	1.60	45.8	
....	....	137								
....	39.2	...	....	....	..	..	..	....	....	Observation vitiated by restlessness
69.0	39.0	...	45.0	....	..	..	..	1.68	51.3	
69.7	38.9	...	43.0	....	..	..	..	1.68	51.4	
....	....	120								
....	37.2	...	....	....	..	..	..	....	....	Afebrile, basal, moved in last 4 min. of last period
58.2	37.2	...	39.5	0.84	8	52	40	1.02	34.7	
70.5	37.2	...	50.0	0.75	7	77	16	1.17	39.9	
....	....	82								
....	39.8	...	....	....	..	..	..	....	....	Restless, coughing
65.2	39.4	...	43.0	0.76	2	80	18	1.68	51.7	
4.4	39.2	...	36.0	0.79	2	70	28	1.58	48.8	
....	....	120								

TABLE 7.—Calorimetric—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period, Time	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
Anna H.	Prelim.	12:25	....	....	....	....	....	....	....
2/5/20	1	1:25⟩							
41.0 Kg.	2	2:25⟨	45.5	47.3	0.76	62.9	0.46	143.9	138.2
1.41 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
John H.	Prelim.	11:50	....	....	....	....	....	....	....
2/10/20	1	12:50	21.6	20.1	0.78	37.5	....	66.8	69.0
45.5 Kg.	2	1:55*	23.9	23.7	0.73	35.3	....	77.8	71.9
1.53 Sq. M.									
John H.	Prelim.	11:54	....	....	....	....	....	....	....
2/12/20	1	12:54	24.1	23.4	0.75	34.6	0.42	76.6	71.6
45.1 Kg.	2	1:54	25.5	25.1	0.74	40.3	0.42	82.2	77.7
1.53 Sq. M.	3	2:54	26.5	26.5	0.73	43.6	0.42	86.5	81.7
	Aver.	.....	....	....	....	....	....	....	....
John H.	Prelim.	1:19	....	....	....	....	....	....	....
3/1/20	1	2:19	21.4	21.6	0.72	30.6	....	70.5	63.9
44.9 Kg.									
1.53 Sq. M.									
John H.	Prelim.	1:22	....	....	....	....	....	....	....
4/14/20	1	2:22	19.9	17.8	0.82	48.9	....	59.6	75.2
44.7 Kg.	2	3:22	20.8	20.0	0.76	47.2	....	66.3	69.6
1.53 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Wm. H.	Prelim.	12:15	....	....	....	....	....	....	....
3/2/20	1	1:15	23.0	21.5	0.78	34.9	0.34	71.2	76.6
50.3 Kg.	2	2:15	23.2	22.6	0.75	33.8	0.34	74.2	75.5
1.53 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Wm. H.	Prelim.	12:00	....	....	....	....	....	....	....
3/10/20	1	1:00	20.8	19.4	0.78	31.4	0.30	64.4	72.1
49.7 Kg.	2	2:00	21.5	20.2	0.78	30.3	0.30	66.8	70.6
1.53 Sq. M.									
Wm. H.	Prelim.	11:27	....	....	....	....	....	....	....
3/11/20	1	12:27	21.8	21.0	0.75	40.0	0.65	68.7	73.1
49.7 Kg.	2	1:27	24.0	22.5	0.77	32.4	0.65	73.9	70.5
1.53 Sq. M.	3	2:27	27.4	26.3	0.76	33.9	0.65	86.1	76.1
	Aver.	.....	....	....	....	....	....	....	....
John S.	Prelim.	12:37	....	....	....	....	....	....	....
3/17/20	1	1:37	26.9	22.9	0.86	41.4	....	77.6	83.6
62.3 Kg.	2	2:37	27.1	28.0	0.71	51.9	....	91.5	92.3
1.88 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Geo. M.	Prelim.	11:20	....	....	....	....	....	....	....
3/24/20	1	12:20	26.1	24.3	0.78	41.5	....	80.8	81.2
49.2 Kg.	2	1:22*	25.1	22.6	0.81	48.0	....	76.1	90.4
1.53 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Geo. M.	Prelim.	11:22	....	....	....	....	....	....	....
3/26/20	1	12:22	27.4	23.1	0.86	43.9	....	78.4	80.0
48.9 Kg.	2	1:22	25.8	23.2	0.81	61.6	....	77.5	101.6
1.53 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Joseph R.	Prelim.	12:27	....	....	....	....	....	....	....
5/25/20	1	1:27	23.5	21.2	0.81	29.7	0.20	71.0	60.5
61.3 Kg.	2	2:27	23.1	21.1	0.80	29.5	0.20	70.4	64.1
1.74 Sq. M.	Aver.	.....	....	....	....	....	....	....	....

—Data—(*Continued*)

Direct Calorimetry Rectal Temp., Cal.	Rectal Temp., C.	Average Pulse	Work Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohydrate	Per Kg.	Per Sq. M. Linear	
....	39.4	.								
	{ 39.5	...	21.0 }							
146.3	{ 39.6	...	21.0 }	0.74	17	73	10	....	....	Fairly quiet
....	....	132	....	....	..	..	..	1.76	51.1	
....	37.4	...	....	....	..	..	..	....	....	(* 65 min.) Basal
65.2	37.3	...	8.5	....	..	..	..	1.47	43.7	
74.6	37.4	...	11.0	....	..	..	..	1.57	46.7	
....	37.9	...	....	....	15	75	10	....	....	350 gm. meat given 1 hour before start
72.0	37.9	...	30.0	0.74	15	75	10	1.70	50.0	
79.5	38.0	...	20.0	0.73	14	79	7	1.82	53.7	
84.2	38.1	...	37.0	0.72	13	57	30	1.92	56.5	
....	....	93								
....	38.7	...	....	....	..	..	..	....	....	Basal
64.6	38.7	...	18.0	....	..	..	..	1.57	46.1	
....―	37.8	...	....	....	..	..	..	....	....	Basal
60.5	37.4	...	3.0	....	..	..	..	1.33	39.0	
72.4	37.5	...	11.0	....	..	..	..	1.48	43.3	
....	....	104								
....	38.6	...	....	....	..	..	..	....	....	Basal in first hour, coughing in second hour
76.3	38.6	...	18.5	0.78	13	67	20	1.41	46.5	
75.9	38.6	...	35.5	0.74	12	78	10	1.47	48.5	
....	....	80								
....	38.0	...	....	....	..	..	..	....	....	Basal
72.2	38.0	...	8.5	0.78	12	68	20	1.32	42.1	
71.0	38.0	...	11.0	0.77	12	69	19	1.49	48.5	
....	37.6	...	....	....	..	..	..	....	....	350 gm. meat given 1 hour before start
64.0	37.4	...	3.5	0.74	23	70	7	1.38	44.9	
76.3	37.5	...	14.0	0.76	20	65	15	1.49	48.3	
88.1	37.8	...	24.0	0.75	25	66	9	1.73	56.3	
....	....	85								
....	37.8	...	....	....	..	..	..	....	....	Basal
83.7	37.9	...	10.0	....	..	..	..	1.25	41.3	
69.4	37.4	...	32.0	....	..	..	..	1.47	48.7	
....	....	114								
....	39.6	...	....	....	..	..	..	....	....	(* 62 min.) Falling temperature, restless
74.5	39.4	...	25.0	....	..	..	..	1.64	52.8	
61.8	38.7	...	30.0	....	..	..	..	1.46	48.1	
....	....	94								
....	39.2	...	....	....	..	..	..	....	....	Rapid fall of temperature, restless
63.3	38.8	...	40.0	....	..	..	..	1.60	51.2	
74.2	38.2	...	40.0	....	..	..	..	1.59	50.6	
....	...	84								
....	36.7	...	....	....	..	..	..	....	....	Basal
62.2	36.8	...	17.0	0.81	8	60	32	1.16	40.8	
58.7	36.7	...	12.0	0 80	8	64	28	1.15	40.5	
....	....	88								

In the remaining observations, which were not basal, it will be observed in Table 8 that the heat production may be considerably increased by coughing, restlessness and by high fever. The increase in metabolism is usually due to several factors combined and it is, of course, impossible to evaluate each factor. The greatest increase in any single hour reached 43 per cent. above the average normal in the case of Trellis H., whose temperature was over 40 C. and who was coughing. In one observation on William H. the temperature remained stationary at 38.6 C. during two hours in the first of which
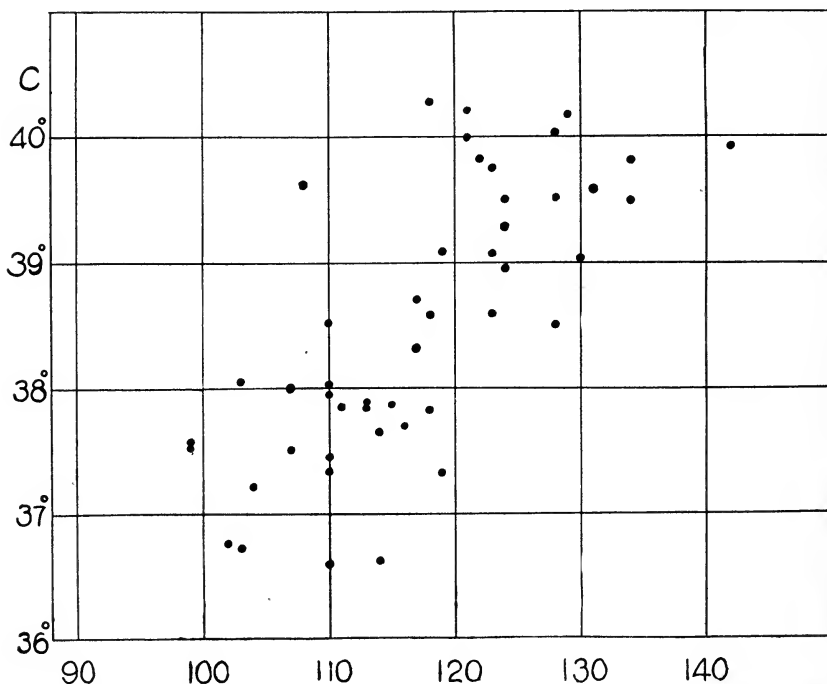
Fig. 13.—Relationship of body temperature and heat production in tuberculosis. The metabolism, during a short period, expressed in terms of percentage of average normal (100 per cent.) is plotted against the mean rectal temperature for the same period, which was usually one hour.

the patient was very quiet and the metabolism was 18 per cent. above the average normal. In the second hour he was likewise very quiet but coughed considerably, with the result that a further increase of 5 per cent. in metabolism occurred.

In Figure 13 an attempt has been made to evaluate the effect of body temperature on the heat production. In the figure the spots represent the percentage of average normal metabolism in a given period, usually one hour, plotted against the average rectal temperature for the period. The grouping of these points suggests the

general tendency of an increased body temperature to increase the heat production. In the case of Robert W. the patient was very quiet at a temperature ranging between 40.1 and 39.4 C., the metabolism being 29 per cent. above average normal. Also, in one hour Trellis H. was very quiet, with a temperature of from 40.1 to 40.2 C., his metabolism being 29 per cent. above average normal. In these two cases the effect of temperature is uncomplicated.

In Figure 14 there is a graphic representation of the relationship of heat produced in the body to the heat eliminated from the body in five cases, chosen to illustrate different phases of temperature change. In the case of Edith B., the temperature rose from 37.3 C. to 38.3 C. during two hours, without a chill. It will be observed that during this rise of 1 degree the heat production rose only a little over two calories per hour. During the first hour the heat eliminated was 9 calories less than the heat produced, and during the second hour the elimination of heat was about 2 calories less than in the first, still further increasing the storage of heat.

The question of the mechanism of temperature changes in the body is of great interest. A review of the literature on this subject will be found in a paper by Barr and Du Bois.[26] In the metabolism of malaria the rise in temperature was accompanied by a chill and a part of the rise in heat production may therefore be attributed to the muscular work of shivering. The case of Edith B., therefore, may be contrasted with the malarial paroxysm, since in her case the rise was not accomplished by a chill, nor by much increase in metabolism, the heat radiated being reduced. Referring again to Figure 14, it will be noticed that on a subsequent occasion with a much higher temperature her metabolism during the first hour showed almost no further increase over that of the first observation. During the second and third hours she was coughing and restless. These observations show that increases in metabolism due to elevation of body temperature, per se, may not be large.

In this same observation and in a subsequent one on the same patient the peak of the rise in rectal temperature was included. Though the rectal temperature had started to drop in the third hour of each experiment, the heat eliminated from the body had not yet exceeded the heat produced. Thus, it appears that for a short time, at least, the average body temperature was still rising after the rectal temperature began to fall.

The fourth observation, graphically presented in Figure 14, shows a rapid fall of temperature with sweating. Here the heat lost greatly

26. Barr, D. P., and Du Bois, E. F.: The Metabolism in Malarial Fever, Arch. Int. Med. **21**:627 (May) 1918.
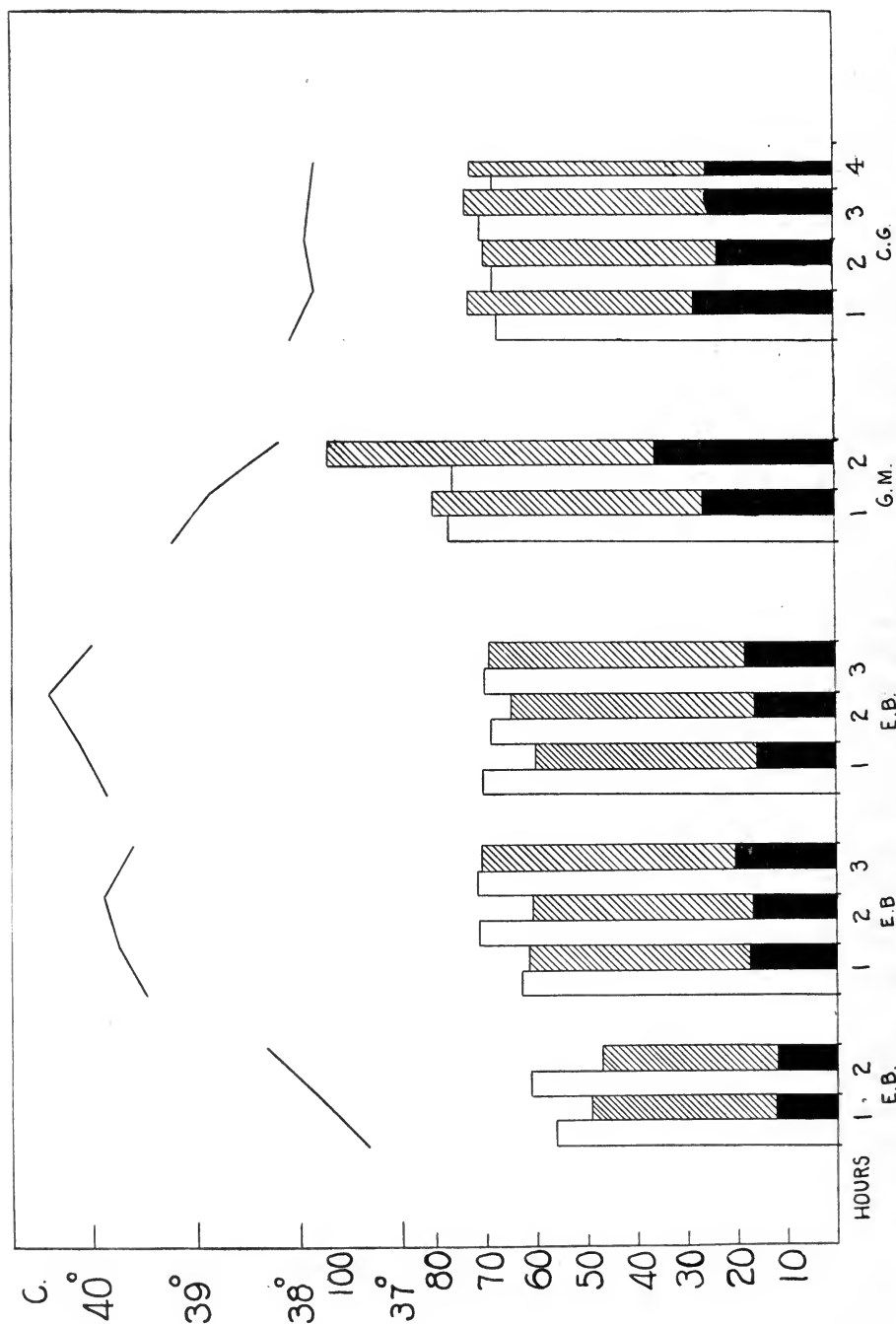
Fig. 14.—Relationship of heat production and heat elimination during rise and fall of rectal temperature. Five observations on three individuals. Lines show rectal temperature in degrees C. Unshaded columns represent calories per hour produced in the body, determined by the indirect method. Shaded columns represent heat lost from the body by vaporization of water (solid black) and by radiation (hatched). Periods are one hour for each pair of columns.

exceeded the heat produced, and the average body temperature fell with the rectal temperature. In this observation a great increase occurred in the number and percentage of calories lost by vaporization of water from the skin and lungs. Du Bois[27] has shown that under ordinary circumstances the water elimination from these sources requires about 25 per cent. of the total heat for its vaporization. In the case of George M. the percentage was between 32 and 35. In the observation of Charles G., shown in the same figure, the latent heat of vaporization amounts to 38 per cent. of the total. This observation was made at the end of a fall in temperature and it will be noted that the average body temperature continued falling after the rectal temperature had become almost stationary. These observations show that the rectal temperature is not an entirely reliable index of changes of the average body temperature and that the absolute relation between the two remains unknown.

In this connection it should be pointed out that the heat produced, as calculated in the direct calorimetry, is equal to the heat eliminated plus or minus the body change correction. This body change correction is estimated by multiplying the change in rectal temperature in degrees centigrade by the specific heat of the body (0.83) times the body weight in kilograms. For the year 1919-1920 the total number of calories measured indirectly was 6,511.73, the total heat eliminated was 6,441.60 calories, while the total heat produced measured by the direct calorimetry, corrected for changes in rectal temperature, was 6,167.37. Such a discrepancy may be accounted for partly by the lack of parallelism between the rectal and average body temperatures and the fact that the total fall in rectal temperature exceeded the total rise.

THE SPECIFIC DYNAMIC ACTION OF PROTEIN IN TUBERCULOSIS

Two of the patients in this series were given a meal of meat in order to study the effect of the protein on the heat production. Various meals have been used in the past for this purpose, but in the present instance the meal consisted of 350 gm. of lean beef, ground, pressed into balls, and cooked in 10 gm. of butter. This gave 70 gm. of protein, 28 gm. of fat and 547 total calories. The observation in each case was started one hour after the middle of the meal and continued for three hours. The rise in heat production compared with the basal heat production is shown graphically in Figure 15..

The average increase in metabolism per hour for three hours was 16.1 per cent. in the case of William H. and 18.4 per cent. in

27. Soderstrom, G. F., and Du Bois, E. F.: The Water Elimination Through the Skin and Respiratory Passages, Arch. Int. Med. **19**:931 (June) 1917.

the case of John H.   In the first case the extra heat in the fourth
hour after eating amounted to 31 per cent. of the basal metabolism
and in the second case to 25 per cent.   The effect of the same meal
has been studied on three normal men.   So far, the behavior of the
tuberculous patients has differed in no way from that of normals.
Further study of the effect of this protein meal, both on tuberculous
and normal subjects, will be the subject of a later communication.

With the normal subject with the same meal the average per-
centage increases in the second, third and fourth hours, respectively,
were, 16, 24 and 24 per cent.   The average increase per hour was
21 per cent.   There were considerable variations among the normals
studied, probably due to differences in the rate of digestion and
absorption.   The effect of the meal has been observed on one normal
to the end of the fifth hour after eating, in which the metabolism
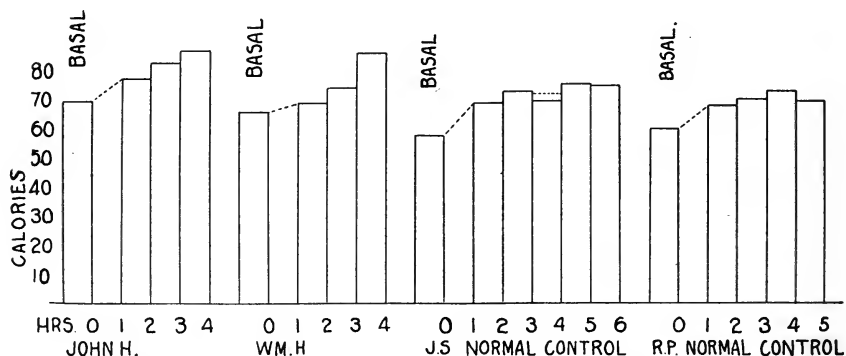
Fig. 15.—Effect of a protein meal on the heat production.

was still 30 per cent. above the basal level, with an average hourly
increase of 25 per cent.   It seems probable that the effect of the
meal would persist for from nine to ten hours at least.

It is to be remembered that Coleman and Du Bois [28] found very
little specific dynamic action of protein in febrile typhoid patients.
They point out that the protein metabolism was at high level at
the time of the basal observation, due to the influence of the disease,
and that the protein ingested merely served to replace protein already
breaking up in increased quantity, and such protein would not serve
to increase the heat production.   The fact that a specific dynamic
rise has been noted in tuberculosis is further evidence that the toxic
destruction of protein is less than in typhoid fever.

28. Coleman, Warren, and Du Bois, E. F.:   Calorimetric Observations on
the Metabolism of Typhoid Patients With and Without Food, Arch. Int. Med.
15: Pt. 2, 940 (May) 1915.

THE PROTEIN MINIMUM IN TUBERCULOSIS

The minimum protein requirement in tuberculosis probably depends, as in health, on the size of the "wear and tear" quota and an adequate supply of nonprotein foodstuffs. Investigations of other infections have shown generally an increase in protein destruction due to the toxins of the disease. Some evidence [2] has been given regarding the extent of this toxic destruction, which indicates that it is small but of importance because of the great duration of the disease.

The work of Chittenden, Sivén, Kumagawa and many others [29] indicates that the protein metabolism of normal men may be reduced to a very low level. More recently Sherman [30] has found from 0.633 to 0.637 gm. of protein per kilogram of body weight per diem to be adequate for the maintenance of normal men.

In typhoid fever Kocher [31] has studied the toxic destruction of protein by giving to a patient a diet containing carbohydrate in large amounts and very little protein. He found it impossible, during the febrile period, to reduce the protein metabolism to the low level of the normal "wear and tear" quota.

In four of the cases of our series, observations were made which were somewhat similar to those of Kocher. The estimated daily basal requirement for each case is given in Table 8. The records of the amounts of food given and of the nitrogen balances are to be found in Tables 3 to 6, inclusive, and are shown graphically in Figures 16 to 19, inclusive. In general, the procedure was to give the patient a diet slightly in excess of the basal energy requirement, containing between 10 and 15 gm. of nitrogen per diem for a period of five or six days. The nitrogen intake was then reduced, with a simultaneous increase in the amount of fat and carbohydrate.

The data obtained in these four cases are insufficient to establish the minimum requirement of protein for tuberculous patients. They will serve as a starting point for work of a similar nature, on which a later report will be made. In general it may be said that when the food nitrogen was reduced to the low level of from 3 to 3.5 gm. per diem, with the addition of from 600 to 900 calories to the basal requirement, the urinary nitrogen excretion fell to the level of 5 or 6 gm. per diem, the patient remaining in negative nitrogen balance. This indicates a "wear and tear" quota greater than normal. The minimum nitrogen excretion noted by Kocher [31] in a typhoid patient was somewhat higher (10.4 gm. during fever, from 5.8 to 6.7 gm. beginning convalescence) and was obtained at the expense of much

29. Chittenden, Russell H.: Physiological Economy in Nutrition, 1914.
30. Sherman, H. C.: Protein Requirement in Maintenance of Man, J. Biol. Chem. **41**:97, 1920.
31. Kocher: Deutsch. Arch. f. klin. Med. **115**:106, 1914.

more carbohydrate and fat. A toxic destruction of protein exists, therefore, in tuberculosis but to less extent than in typhoid fever.

In view of the results in these four cases, it seems probable that many febrile, tuberculous patients may be kept in nitrogen balance on diets containing from 60 to 70 gm. of protein per diem. The
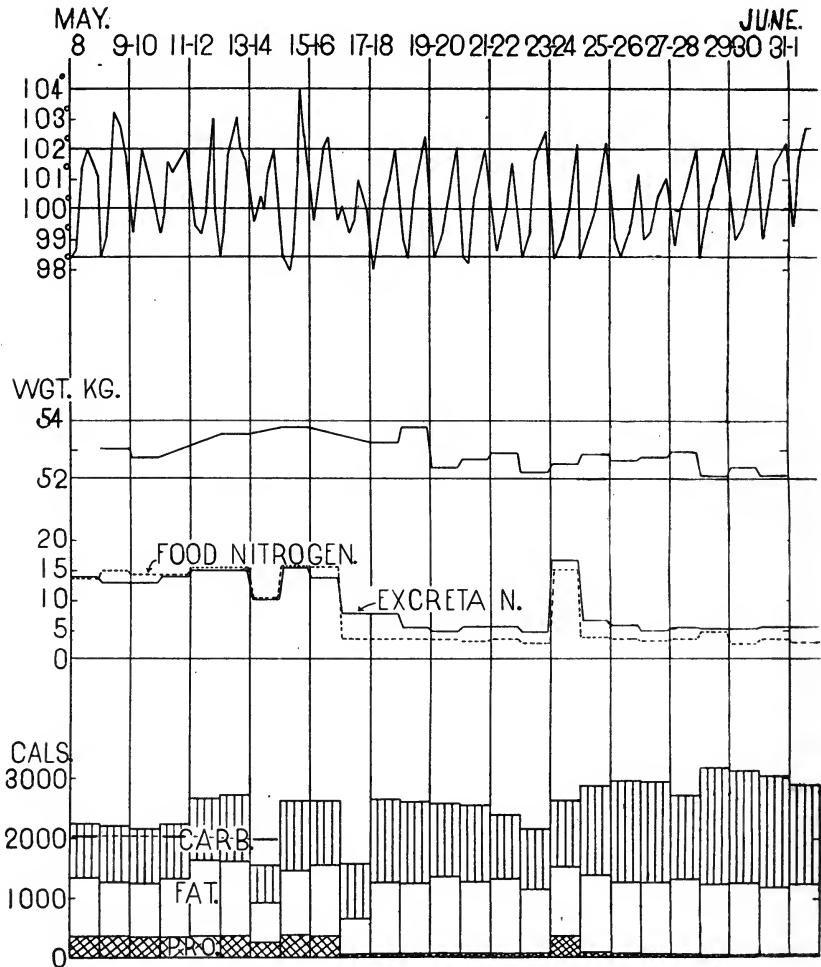
Fig. 16.—Diet chart and nitrogen balance, Charles G.

amount of protein is much less than Voit's standard allowance (118 gm.) for normal men, though somewhat greater than the normal minima of Chittenden and of Sherman (from 35 to 45 gm.). It is much less than is fed to patients in many of the sanitaria for tuberculosis.

Fig. 17.—Diet chart and nitrogen balance, George P.
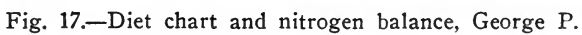
PRACTICAL CONSIDERATIONS REGARDING DIET IN TUBERCULOSIS

The importance of rest during periods of activity of pulmonary tuberculosis has been generally recognized. By artificial pneumothorax, by rest, by control of the cough, the volume of the respiratory exchange and of the total ventilation is reduced. This seems to be a desirable end for which to strive during the period of encapsulation of the foci of the disease. It does not seem to have occurred to the practitioner that an increase in metabolism due to the specific dynamic action of protein will have the same effect on the respiratory exchange as a similar increase due to muscular work.

TABLE 8.—SUMMARY OF CALORIMETER DATA

Name	Weight in Health, Kg.	Surface in Health, Sq. M.	Estimated Calories per Hour in Health	Present Calories per Hour Observed	Present Surface Area, Sq. M.	Metabolism Variation from Aver. Normal per Cent.	Calories per 24 Hours	Remarks
Chas. G.	....	....	. ..	69.5	1.56	+13	1,668	Basal
Trellis H.	....	....	....	84.4	1.57	+35	2,026	Fever, 40 C.; cough
Robert W. ...	....	....	....	78.6	1.57	+29	1,886	40.1–39.4 C., quiet
Geo. P.	69.5	1.84	75.4	75.5	1.70	+11	1,812	Basal
Spencer C. ...	74.0	1.85	71.2	63.9	1.48	+12	1,534	Basal
Edith B.	61.5	1.77	66.4	59.0	1.53	+ 2	....	Basal, afebrile
				66.6	1.53	+15	1,598	Fever, restless
Harry G.	56.0	1.60	68.8	73.5	1.40	+21	1,746	Fever, restless
Joseph D. ...	61.3	1.75	67.4	64.9	1.74	− 3	1,558	Basal
Anna H.	51.0	1.55	62.0	72.0	1.41	+28	1,728	Fever, coughing
Mich. C.	59.0	1.74	68.7	81.5	1.62	+27	1,956	Fever, coughing
John H.	64.5	1.78	70.3	69.9	1.53	+15	1,678	Basal, febrile
				63.0	1.53	+ 5	1,512	Basal, afebrile
Wm. H.	61.0	1.67	66.0	65.6	1.54	+ 9	} 1,658	Basal, 38 C.
				72.7	1.53	+21		Coughing, 38.6 C.
John S.	76.0	2.04	80.6	84.6	1.88	+14	2,030	Basal
Geo. M.	62.3	1.69	66.8	77.6	1.53	+28	1,852	Fever, restless
Joseph R. ...	82.0	1.98	78.4	70.7	1.74	+ 3	1,697	Basal
J. D.	....	....	....	61.8	1.50	+ 4	1,483	H. G. Barbour's case
G. G.	....	....	....	62.4	1.54	+ 3	1,598	Same
S. L.	....	....	....	67.2	1.63	+ 4	1,613	Same

* Average of two operations.

During periods of acute activity of the disease it may be well to limit the protein intake and the total calories fed to patients to the minimum necessary to maintain nitrogen equilibrium without regard to the weight of the patient. Later, when acute symptoms have subsided, and when there is evidence that the natural barriers against the disease are established, a more liberal diet could be given with less fear of the effects of an increased respiratory activity.

An excellent article has just appeared, by Janney and Newell,[32] on the relationship of tuberculosis and diabetes. These authors point out that the course of pulmonary tuberculosis, complicating

32. Janney, N. W., and Newell, R. R.: Treatment of Diabetes Complicated by Pulmonary Tuberculosis, J. A. M. A. **75**:153 (July 17) 1920.

diabetes, does not seem to be influenced unfavorably by the state of undernutrition resulting from a rigid adherence to the proper diabetic diets, but quite the reverse. They show that among diabetic patients the mortality rate from tuberculosis has diminished markedly since the inauguration of the Allen treatment. Similar experience has also been recorded by Joslin.[33] In their own series of cases the development of tuberculosis seems always to have commenced during periods in which diabetic patients were living on a liberal and uncontrolled dietary. In view of these facts no unfavorable results are to be expected from temporary dietary restrictions in nondiabetic tuberculous patients.
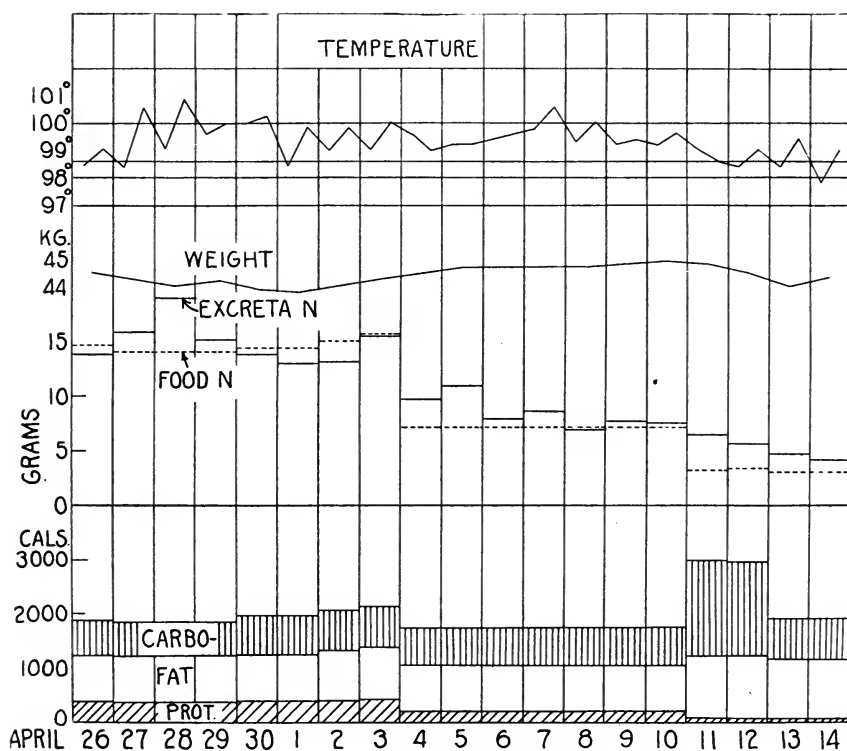
, Fig. 18.—Diet chart and nitrogen balance, John H.

In Table 8 estimates of the daily heat production of patients in this series are given. These range from 1,500 to 2,000 calories per day for rest in bed and the fasting state. During periods of activity of a pulmonary tuberculosis the diet need not contain more than 500 calories above the basal requirement (from 2,000 to 2,500 calories), nor more than 60 gm. of protein. The object of such a diet is to maintain the respiratory activity at the lowest level compatible with

33. Joslin: The Treatment of Diabetes Mellitus, 1916.
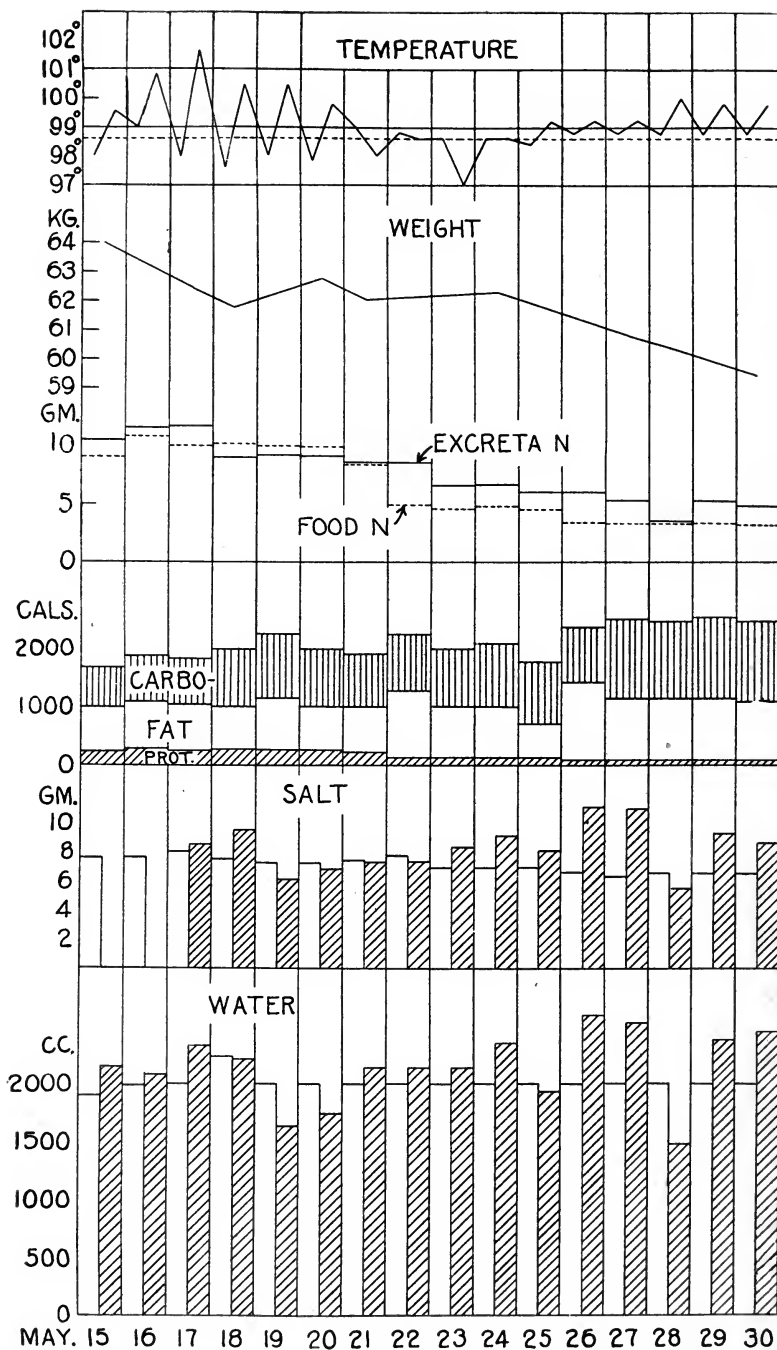
Fig. 19.—Diet chart and nitrogen balance, Joseph R. Water formed by combustion and that eliminated from skin and lungs was not included in the measurement of water balance. Water and salt output in shaded columns. Intake unshaded.

the maintenance of nitrogen equilibrium. To achieve this purpose it is just as necessary not to overfeed as it is to maintain muscular rest.

When the activity of the disease has subsided the total calories in the diet should be raised to meet the requirements of the patient as his muscular activity increases. The protein intake could also be increased to enlarge the repair quota.

SUMMARY

1. The basal metabolism of tuberculous patients may be normal or very slightly above that of normal men of the same size. Thus, in ten cases, the variation from average normal was from minus 3 to plus 15 per cent.

2. Further increases in metabolism occur with a rise of body temperature. These increases are not large. Thus one case was given in which the temperature rose 1 degree C. during two hours without a chill. The heat production of the second hour was only two calories greater than that of the first hour. With a rectal temperature of 104 F., (40 C.) the metabolism may be 30 per cent. above the average normal.

3. The basal heat production in tuberculosis may be less than the normal for the same patient when in health; in other words, the loss in weight may be accompanied by a reduction in metabolism which more than compensates for the tendency to increase caused by the disease.

4. Limited data regarding the nitrogen excretion show that, while a toxic destruction of protein does exist in tuberculosis, it is not large. The urinary nitrogen may be reduced to from 5 to 6 gm. per diem, though nitrogen balance may be attained only at a higher level (about 10 gm. a day).

5. The specific dynamic rise in metabolism produced in two cases by the ingestion of a protein meal corresponded closely with that produced by the same meal in three normal men.

CONCLUSIONS

In view of the fact that the food requirements of tuberculous patients are not large, either as regards total energy value or nitrogen content, forced feeding is unnecessary and is probably harmful in the active stages of pulmonary disease. Since protein increases the respiratory exchange in the tuberculous as in normals it may be well to limit the protein intake during periods of activity (of the disease) in order to put the lungs at rest.

THE FAILURE OF ANTIBODY FORMATION IN LEUKEMIA *

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A few reported studies on the blood of leukemia patients show that antibodies either do not occur or are lessened in several of the infectious diseases and after inoculation with various organisms.

Moreschi [1] observed that a patient with chronic lymphatic leukemia, who contracted typhoid fever, failed to develop agglutinin for *B. typhosus*. From a study of the literature on typhoid fever, he found that about 6.7 per cent. of typhoid fever patients normally failed to produce agglutinin. In order to determine whether the failure in antibody production in his patient was due to this normal percentage of failure or to the chronic leukemia, he started inoculating his leukemic patients against *B. typhosus* to observe the agglutinin response. In the course of two years he had inoculated two patients with lymphatic leukemia and six with myelogenous leukemia. A lymphatic leukemia patient who contracted typhoid fever and a lymphosarcoma patient with a paratyphoid B. infection also came under his observation during this time. Six of the eight vaccinated patients had no rise in temperature or any of the usual systemic symptoms occurring after typhoid inoculation. The remaining two patients had received roentgen-ray treatment, and they had slight rise in temperature, headache and malaise. In each of the vaccinated cases, the blood was tested for agglutinin before inoculation and again from eight to ten days after inoculation. One of the patients who had had a rise in temperature and one who had been under benzol and roentgen-ray treatment had agglutinin in a 1:20 serum dilution. The other six patients gave no evidence of agglutinin formation. Blood from the chronic lymphatic leukemia patient with typhoid fever and from the lymphosarcoma patient with paratyphoid B. infection had slight agglutinin in 1:10 serum dilution, but none in higher serum dilution.

Rotky [2] used a harmless vibrio which was isolated from water and which in animal experiments showed good agglutinin production. The

1. Moreschi, C.: Ueber antigene und pyrogene Wirkung des Typhusbacillus bie leukämischen Kranken, Ztschr. f. Immunitätsforsch. u. Exper. Therap. **21**: 410, 1914.

2. Rotky, H.: Fähigkeit von Leukämikern Antikörper zu erzeugen, Zentralbl. f. inn. Med. **35**:953, 1914.

action of this organism, one-tenth loop of killed agar culture emulsion injected subcutaneously, was tested on normal and leukemic persons. Eight normal persons tested had a slight local reaction only. One week after inoculation, however, agglutinin was present in a 1:20 serum dilution in all instances, and in a few it rose to 1:500. The one lymphatic leukemia patient and the one myelogenous leukemia patient had severe local reactions of three days' duration. They had slight fever, headache and splenic pain, which was more marked in the myelogenous leukemia patient. The leukocytes were increased in the lymphatic leukemia patient from 16,800 to 35,000, and in the myelogenous leukemia patient from 96,000 to 130,000. One week after injection of the vibrio vaccine, neither case showed any agglutinin in 1:10 serum dilutions.

EXPERIMENTAL OBSERVATIONS

Because of its bearing on the general problem of antibody formation, a more detailed study of the antibodies in a lymphatic leukemic patient and a myelogenous leukemic patient was undertaken. Each patient was inoculated with 0.5 c.c of a triple vaccine [3] containing 1,000 million *B. typhosus,* 750 million *B. paratyphosus* A and 750 million *B. paratyphosus* B per c.c. The blood count and the opsonin and agglutinin for each bacterial species were examined before vaccination and at intervals thereafter.

Agglutinin was examined by the microscopic method. Hanging drops containing suspensions of living organisms and active serums in varying dilutions were incubated 10 minutes at 37 C. before examination for clumping.

Opsonin was estimated by diluting the serum to the point of opsonic extinction. The dilution in which fifty leukocytes had the same per cent. of cells taking part in phagocytosis as a normal control with salt solution was considered the point of extinction. Varying dilutions of active serum, human leukocytes and living bacteria were incubated in capillary tubes at 37 C. for ten minutes. A film was made from each tube and the number of leukocytes taking part in phagocytosis was observed.

The case of lymphatic leukemia was a patient of Dr. C. A. Elliott, to whom we wish to express our appreciation for the privilege of studying the case. This patient was receiving roentgen-ray treatment at the time of vaccination, and radium treatments were started on the twentieth day after inoculation with triple vaccine. The patient had

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3. Dreyer, G.; Gardner, A. D.; Gibson, A. G., and Walker, E. W. A.: Prophylactic Triple Inoculation Against Typhoid and Paratyphoid Fevers, Lancet **1**:498, 1918.

no rise in temperature, headache or other systemic reactions. There was slight redness and swelling at the site of inoculation, and moderate axillary glandular involvement. The white blood count (Table 1) was taken on the day of inoculation and on the fourth, eighth, twelfth, twenty-first and twenty-fifth days thereafter. There was a gradual decline in leukocytes from 325,000 to 228,000. About 99 per cent. of the white cells were small lymphocytes.

TABLE 1.—LYMPHATIC LEUKEMIA

Days After Inoculation With Triple Vaccine	White Blood Count	Agglutinin			Opsonin		
		B. Ty- phosus	B. Para- typhosus A	B. Para- typhosus B	B. Ty- phosus	B. Para- typhosus A	B. Para- typhosus B
0	320,000	0	0	0	0	0	0
4	286,000	0	0	0	0	0	0
8	280,000	0	0	0	0	0	0
12	275,000	0	0	0	0 ·	0	0
21	220,000	0	0	0	0	0	0
25	228,000	0	0	0	0	0	0

0 = no agglutinin or opsonin in undiluted serum.

Opsonin and agglutinin for *B. typhosus, B. paratyphosus* A and *B. paratyphosus* B were observed on the same days that the leukocyte counts were made. At no time did even undiluted serum show the presence of agglutinin or opsonin.

A healthy person injected at the same time with a similar dose of the triple vaccine, had a moderate local reaction, headache and a feeling of malaise, lasting twenty-four hours but no rise in temperature. In this person agglutinin and opsonin were present in high serum dilutions after the twelfth day.

The patient with myelogenous leukemia, who was admitted to the medical service of Michael Reese Hospital, had received no treatment at the time of vaccination. There was a moderate local reaction, one degree rise in temperature, but no other general symptoms. The leukocyte count, agglutinin and opsonin were observed on the day of inoculation and on the second, fourth, seventh, tenth, fourteenth, eighteenth and twentieth days after vaccination. The leukocyte and differential blood counts (Table 2) varied slightly from day to day but were apparently not affected by the vaccine. Undiluted serums agglutinated *B. paratyphosus* A and *B. paratyphosus* B very slightly, but never clumped *B. typhosus.* The point of opsonic extinction, using undiluted serum, was never above the normal salt control, and frequently fewer leukocytes were phagocytic.

A healthy person vaccinated at the same time had a severe local reaction lasting five days, a rise of one degree in temperature, severe

headache and general malaise of two days duration. Agglutinin and opsonin were present in this serum after the tenth day.

DISCUSSION

The results obtained in these two cases correspond to those of Moreschi and of Rotky in that no agglutinin was produced after typhoid vaccination. In addition, opsonin, not investigated by these workers, was absent. A frequent cause of death in both forms of leukemia is intercurrent infection, fatal sepsis due to the more common pyogenic bacteria being not unusual. The resistance of a leukemic person to bacterial invasion appears to be lower than that of a normal person, and this condition may find its explanation in a loss of ability on the part of the leukemic patient to form antibodies.

TABLE 2.—MYELOGENOUS LEUKEMIA

Days After Inoculation With Triple Vaccine	White Blood Count	Differential Blood Count						Agglutinin			Opsonin		
		P.	L.	T. and L. M.	E.	B.	M.	B. Typhosus	B. Paratyphosus A	B. Paratyphosus B	B. Typhosus	B. Paratyphosus A	B. Paratyphosus B
0	42,200	34	9	28	0	0	29	0	0	0	0	0	0
2	42,000	36	7	28	0	0	29	0	0	0	0	0	0
4	42,100	38	2	29	1	5	25	0	S	S	0	0	0
7	37,100	52	2	15	1	0	30	0	S	S	0	0	0
10	42,700	54	10	7	0	0	29	0	S	0	0	0	0
14	56,000	47	7	18	0	0	28	0	S	0	0	0	0
18	36,200	54	14	7	0	0	23	0	S	0	0	0	0
20	43,000	71	2	9	0	8	18	0	S	S	0	0	0

P. = Polymorphonuclear leukocytes.
L. = Lymphocytes.
T. and L. M. = Transitionals and large mononuclears.
E. = Eosinophils.
B. = Basophils.
M. = Myelocytes.
0 = No agglutinin or opsonin in undiluted serum.
S = Slight agglutinin in undiluted serum.

While the prognosis of an infection developing during the course of leukemia is bad, the effect of the infection on the leukemia may be the reverse. It is, perhaps, improper to say that there is any actual improvement in the patient's condition or that his probable duration of life is prolonged by the intercurrent infection if he recovers from the latter, but there may be symptomatic improvement in that the high leukocyte count may be considerably or markedly decreased, an improvement comparable to that brought about by the action of leukocytotoxic agents. This phenomenon has been described by a number of observers, and in a few cases it has been associated with perceptible decrease in the enlarged lymph nodes and spleen. Possibly, the decrease in the leukocyte count may be the result of exhaustion of the hematopoietic tissues by the continuous proliferative process which is characteristic of leukemia, so that these tissues are no longer

able to meet the added stimulus of an acute infection.   Or the involved tissues may be so abnormal as to be unable to respond to the stimulus in a normal manner.   All cases of leukemia do not show this absence of leukocyte increase.   Some patients respond to intercurrent infection with an increase in leukocytes, and Rotky's two vaccinated patients showed marked leukocytic increase; in the lymphatic leukemia patient from 16,800 to 30,000, and in the myelogenous leukemia patient from 96,000 to 130,000.   Definite experimental evidence on the reason for the variable leukocytic reaction is not yielded by the cases studied, although in neither case is there the increase in leukocytes that usually follows injection of typhoid vaccine in normal persons.   On the contrary, the leukocyte count in the case of lymphatic leukemia is a progressively decreasing one, a decrease which simulates that which may occur during an intercurrent infection.   But this patient was under roentgen-ray treatment, and it is safer to conclude that this, rather than the vaccine injection, was the cause of the change noted. The patient with myelogenous leukemia, who had been untreated, shows a decrease on the seventh and eighteenth days, respectively, after injection of the vaccine, but this is so slight as to be most probably only part of the fluctuation in leukocytes which this patient showed while under observation.   While neither case, therefore, showed such a decrease in the number of leukocytes following vaccine injection as is sometimes associated with infection, the fact that the normal increase did not occur is of importance and indicates an inability of the blood forming tissues to react to the stimulus of the injection.

The failure of agglutinin formation, both following spontaneous typhoid and paratyphoid fever, as noted by Moreschi, and following antibacterial vaccination, as noted by Moreschi and Rotky, and the absence of both opsonins and agglutinins following antityphoid vaccination in the two cases here reported, is probably part of the still unsolved problem of the locus of antibody formation.   Experimental work on the negative side of this problem indicates, as has been long held but never absolutely proven, that anticellular antibodies are produced in the hematopoietic tissues, and more especially in that tissue one of whose functions is the formation of polymorphonuclear leukocytes, namely, the bone marrow.   Hektoen [4] and Simonds and Jones [5]

4. Hektoen, L.: The Influence of the Roentgen Ray on the Production of Antibodies, J. Infect. Dis. **17**:415, 1915. Further Studies on the Effects of the Roentgen Ray on Antibody Production, J. Infect. Dis. **22**:28, 1918. Influence of Thorium X on Antibody Formation, J. Infect. Dis. **26**:30, 1920. Further Observations on the Effects of Roentgenization and Splenectomy on Antibody Production, J. Infect. Dis. **27**:23, 1920.

5. Simonds, J. P., and Jones, H. M.: The Influence of Exposure to Roentgen-Rays on the Formation of Antibodies, J. M. Res. **33**:183, 1915. The Effect of Injections of Benzol on the Production of Antibodies, ibid. **33**:197, 1915.

have shown that the roentgen ray, benzol and other agents which cause a pronounced decrease in the circulating leukocytes, most probably through destructive action on the hematopoietic tissues, markedly decrease or completely set aside the formation of antibodies. This is strong evidence, in a negative way, in favor of the view, propounded by Metchnikoff and strongly supported by the French school of immunology, that antibodies are formed in the hematopoietic tissues.

But proof on this point from the positive side has been more difficult to adduce, and there is still question in the minds of some as to whether antibodies are formed by leukocytes and by the tissues from which they come. Bedson[6] showed that injection of nuclein increased the phagocytic activity of the leukocytes. This reaction was fleeting and persisted only during the period of hyperleukocytosis. Tunnicliff[7] found that the leukocytes of aleuronat exudate are more highly phagocytic than those of the circulating blood, and gave as the probable explanation of this effect the younger condition of the exudate leukocytes. More recenly[8] she has shown that injection of leukocytic extract, which causes a hyperleukocytosis, increases the phagocytic activity from twofold to fourfold during the period of hyperleukocytosis.

Hyperleukocytosis and increased phagocytosis with intracellular digestion of the engulfed bacteria might, theoretically, have two diametrically opposite effects on antibody formation. If phagocytic cells are themselves capable of producing antibodies, as originally claimed by Metchnikoff, an increase in their phagocytic activity might lead to an increased secretion of antibodies, by stimulation of the normal mechanism. Bachmann[9] claims to have demonstrated the presence of specific antibodies within leukocytes after typhoid immunization of rabbits. If, on the other hand, the property of antibody formation resides, not in the circulating phagocytes, but in the hematopoietic tissues themselves, the excessive destruction of the antigen in the circulating blood might inhibit or decrease antibody formation by destroying the stimulating substances before they reach the fixed tissues. Stenström's[10] experiments support this view. The injection of normal rabbit leukocytes into a second rabbit leads to hyperleukocytosis and

6. Bedson, S. P.: Analysis of the Effect of Nuclein and Nucleic Acid on the Normal Antibody, J. Path. & Bact. **19**:191, 1914.

7. Tunnicliff, R.: Observations on the Phagocytic Activity of the Leukocytes in Exudates, Tr. Chicago Path. Soc. **8**:108, 1911.

8. Tunnicliff, R.: The Action of Leukocytic Extracts on the Phagocytic Activity of Leukocytes, J. Infect. Dis. **26**:447, 1920.

9. Bachmann, A.: Presence de substances specifiques dans les leucocytes des animaux immunises, C. R. Soc. Biol. **82**:1031, 1919.

10. Stenström, O.: Ueber die einwirkung des exsudatleukocyten auf die Antikörperbildung, Ztschr. f. Immunitätsforsch. u. Exper. Therap. **8**:483, 1911.

increased phagocytosis.   When leukocytes and typhoid bacterial anti-
gen were injected at the same time by Stenström, the formation of
agglutinin and bacteriolysin was decreased or prevented.

In the acute infectious diseases hyperleukocytosis and hyperplasia
of the hematopoietic tissues are associated with an increase in anti-
bodies in the circulating blood.   On a priori grounds the great increase
in the number of circulating leukocytes and the marked hyperplasia
of the blood forming tissues in leukemia should be associated with
antibody increase during acute infection or after bacterial immuniza-
tion.   The opposite has been found to be the case by Moreschi and
by Rotky and in the two cases here reported.   Moreschi considers two
possibilities in explanation of the failure of antibody formation.   The
first is that the large number of circulating leukocytes may change
the antigen, so that its antibody inciting properties are lost before it
reaches the tissues which produce antibodies.   Against this possibility
he placed the fact that no agglutinins were demonstrable in lymphatic
as well as in myelogenous leukemia.   According to the second possi-
bility, the hematopoietic system, which is held to be the site of anti-
body formation, is so severely damaged in leukemia that its power to
produce antibodies is lost.   Stentsröm's experimental work would give
strong support to the first possibility if it could be shown that the
leukocytes of leukemia have the property, under the conditions which
exist in the body in the disease, of taking up and destroying the injected
bacteria.   In both the cases which form the basis of this report, there
was complete absence of opsonin even in undiluted serum.   Change
in the antigen brought about by the large number of circulating leuko-
cytes before the antigen can reach the site of antibody formation must,
therefore, be discarded as an explanation of the failure of antibody
formation in leukemia.

Absence of antibodies in leukemia would appear to be due to the
profound alterations which the hematopoietic system undergoes in the
disease.   The nature of the pathologic process which brings about
these alterations is not yet understood, but in a number of respects
the process suggests a neoplastic condition.   Even if the neoplastic
nature of the process is not accepted, the rate of proliferation in the
hematopoietic tissues is so great that the phenomenon which Adami
considers so characteristic of malignant tumors, namely, the loss of
the habit of function and the assumption of the habit of growth,
which after all is merely an expression of rapid proliferation, must
have great influence on the functional capacities of the hematopoietic
tissues and of the cells derived from them.   If antibody formation is
one of the functions of these tissues, then it is fair to assume that
this function is greatly interfered with or set aside by the proliferative

process which characterizes leukemia. Tunnicliff's conception that the increased phagocytosis of aleuronat exudate leukocytes is due to their younger condition, is not opposed to the view stated, because these leukocytes have been produced by the action of a normal mechanism and not by a process so abnormal as that which is present in leukemia. The failure of the highly abnormal hematopoietic tissues of leukemia to produce antibodies is further evidence, again in a negative way like the action of the roentgen ray and benzol, that the normal site of antibody formation is in the blood forming tissues. When the abnormal proliferation of leukemia is more or less completely inhibited by the roentgen ray, benzol, or otherwise, then the patient may respond with more nearly normal reactions. Two of Moreschi's vaccinated patients under roentgen-ray treatment agglutinated typhoid bacilli in a 1:20 serum dilution and several reacted with a rise in temperature. The patient with lymphatic leukemia whose case is reported here was under roentgen-ray treatment, but there was no formation of agglutinin or opsonin. This failure of antibody production cannot be attributed to the roentgenization. Whereas, the roentgen ray in a normal animal interferes with antibody formation through its destructive action on the hematopoietic tissues, in a leukemic individual it should aid in antibody formation, as Moreschi found to be the case to a slight degree, through inhibition of the excessive proliferation of the same tissues.

Moreschi attempts to correlate the absence of temperature reaction after bacterial vaccination with the failure of antibody formation. The untreated patients vaccinated by him formed no agglutinin and had no rise in temperature, while several of his patients under roentgen-ray treatment had a slight temperature rise that was either delayed or of short duration. The leukemic patients vaccinated by Rotky with the water vibrio had slight fever. Of the two cases described here, the untreated myelogenous leukemia patients had a rise in temperature of one degree, the same temperature reaction that was shown by the healthy person used as a control, while the lymphatic leukemia patient who was under treatment, had no rise in temperature. It would seem, therefore, that the temperature reaction in leukemia after vaccination is variable and is not necessarily dependent on the antibody reaction. In the normal individual the temperature increase which follows the injection of a bacterial vaccine may be the expression of the increased metabolism and of the chemical changes which result in the formation of antibodies. But in leukemia, in which irregularities in the temperature curve are not unusual, the rise of temperature which may follow the injection of a bacterial vaccine need not be associated with antibody formation and may be the effect of an action on some factor other than that concerned in the production of antibodies.

SUMMARY

Individuals with leukemia who contract typhoid or paratyphoid infection may fail to develop the specific agglutinins in the blood.

A similar failure of agglutinin formation also occurs when a leukemic individual is injected with typhoid vaccine in a dosage which causes agglutinin formation in a normal control.

Opsonins are also absent in the blood after injection with typhoid vaccine.

The failure of both opsonin and agglutinin formation after typhoid vaccination, as shown in the two cases reported here, of agglutinin formation in Moreschi's spontaneously infected cases and in his vaccinated cases, and of agglutinin production after vaccination with still another bacterial species, as shown by Rotky, may indicate that the tissues of the leukemic individual have lost the property of antibody formation in general.

The loss of ability to form antibodies is probably the result of the marked alterations in the hematopoietic tissues which characterize leukemia. This loss of ability may be due to the excessive proliferation of the hematopoietic tissues, one of whose normal functions is the formation of antibodies. With rapidly repeated cell generations the cellular energy used in multiplication prevents the utilization of the energy which is necessary for normal function.

The temperature reaction after bacterial vaccination in leukemia is variable. When a rise in temperature occurs, it may not be associated with antibody production.

The leukocytic reaction after vaccination is also variable. Some cases react like normals with an increase in the number of circulating leukocytes. Others show no changes. In still others a decrease may occur. The variable leukocytic reaction, like the failure of antibody formation, is probably the result of the alterations in the hematopoietic tissues.

PRIMARY MESOTHELIOMA OF THE PLEURA

A CLINICAL AND PATHOLOGIC CONTRIBUTION TO PLEURAL MALIGNANCY, WITH REPORT OF A CASE *

ERNEST S. DU BRAY, M.D., AND F. B. ROSSON, M.D.

SAN FRANCISCO

Primary neoplasms of the pleura are among the very rare tumors. They occur considerably less frequently than primary growths of the lung or bronchi. Clinically and pathologically the malignant tumors of the pleura form the most interesting and important group. The pathogenesis and consequently the nomenclature of these tumors is still in confusion. Wagner,[1] in 1870, described the classical pleural tumor under the name "tuberkelaehnliche lymphadenome," which opened a long controversy. Schultz,[2] in 1875, reexamined the preparations of Wagner and gave a complete description of the above tumor, emphasizing the neoplastic nature of the growth and naming it "endothelial cancer." These two papers mark the beginning of a stubborn contention which, fifty years after its inception, still remains unsettled. Among the other designations which have been used to describe malignant pleural tumors may be mentioned: lymphangitis proliferans (Fraenkel, Schweninger); lymphangitis carcinomatodes (Neelson); sarcocarcinoma (Boehme), alveolar endothelial sarcoma (Podak), endothelioma (Eppinger and many others), carcinoma (Lepine, Benda, Dreesen, Ribbert, Orth, Sprunt, and Bayne-Jones). Bayne-Jones,[3] in 1919, in reviewing this controversy, aptly states that "this confusing terminology indicates that in the minds of the describers of the tumor there have been two uncertainties. These questions were: (1) What is the origin of the tumor? From the lining cells of the pleura or from the intima of the lymphatics? (2) What is the nature of the cells lining the pleura?"

Benda[4] and Sprunt[5] found areas in their sections in which transitions from the flat cells of the pleural lining to the villous and tubular arrangements of the large cells of the tumor could be seen. These

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1. Wagner: Arch. d. Heilk., 1870 and 1874, p. 634.

2. Schultz, R.: Endothelcarcinom, Arch. d. Heilk. **17**:1, 1876.

3. Bayne-Jones, S.: Carcinoma of Pleura with Hypertrophic Osteo-Arthopathy, Johns Hopkins Hosp. Rep. **18**:213, 1919.

4. Benda, C.: Ueber das primäre carcinom der pleura, Deutsch. med. Wchnschr. **23**:324, 1897.

5. Sprunt, T. P.: Primary Carcinoma of Pleura, Johns Hopkins Hosp. Bull. **22**:289, 1911.

observations suggest that their tumors arose from the lining cells of the pleura. The present view of most histologists is that the lining cells of the pleura are epithelial-like cells derived from the mesoderm when this layer splits to form the pleural cavity. If this is the case those pleural tumors which can be shown to be derived from the lining cells of the pleura may be regarded as epithelial tumors, or carcinomata. The chief difficulty in such determinations is, as Ribbert points out, that examination is never possible in the early stage of the process and must be made when the growth is far advanced and the whole pleura is involved. Adami [6] introduced a new terminology for these tumors. He designated them as mesotheliomas originating from the mesothelial lining of the serous cavity, which in turn, is derived from the mesoderm.

Adler,[7] in his splendid monograph on the primary malignant growths of the lungs and bronchi, takes the stand of Klaatsch [8] and is opposed to an ironclad classification of tumors based on their embryologic relations to the three germinal layers. He believes that embryology is tending more and more toward giving up the mesoderm as a primary germinal layer and is depending more and more on the entoderm and the ectoderm, with only secondary and varying assistance from a secondary mesoderm. He emphasizes the fact that functionally and physiologically endothelium appears closely related to typical epithelium. He agrees with Borst that there are tumors undoubtedly taking origin from endothelium, and, as the endothelium occupies a peculiar position, on the one hand, appropriating to itself some of the functions of epithelium, and on the other hand, being intimately associated with connective tissue, even forming fibroplastic cells, it is best to call these tumors by the special name endotheliomas. Adler states that he has never been convinced of the occurrence of primary malignant endothelioma in the lung itself, but he thinks such tumors undoubtedly do occur in the pleura.

The majority of observers, however, have followed Schultz and Eppinger and regard the origin of these neoplasms as being from the endothelial lining of the pleural lymphatics.

It is well known that vascular metastases are uncommon. Invasion occurs by direct extension through the lymphatics into the lung, pericardium, diaphragm, peritoneum and omentum, and implantation metastases are found frequently on the surface of the organs lying

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6. Adami, J. G.: Principles of Pathology **1**:812, Philadelphia, Lea & Febiger, 1908.

7. Adler, I.: Primary Malignant Growths of Lungs and Bronchi, New York, Longmans, Green & Co., 1912.

·8. Klaatsch, H.: Ueber den jetzigen Stand der Keimblattfrage mit Rücksicht auf die Pathologie, München. med. Wchnschr. **46**:169, 1899.

in the cavities into which the tumor has penetrated. This peculiar manner of extension suggested the possibility of an inflammatory nature of the process to some observers (Neelson, Perls, Fraenkel, Birch-Hirshfeld) and led Schweninger [9] in 1878 to designate the condition, "lymphangitis proliferans."

CLASSIFICATION OF PLEURAL TUMORS

Pallasse and Roubier [10] adopt the classification of all pleural tumors advocated by Guyot and Parcelier which is as follows:

(1) BENIGN GROWTHS: The benign tumors include the usual neoplasms which occur in other tissues, such as lipomas, chondromas and fibromas.

(2) MIXED GROWTHS: Several of these are described: for example, the chondrosarcoma (Ribbert). These neoplasms originate as benign tumors but tend to develop malignant characteristics.

(3) MALIGNANT GROWTHS PROPER: These are classified by M. Mentrier (in Traité de méd. Brouardel-Gilbert) and subsequently by Bloch [11] in his excellent monograph on this whole subject into two large subgroups, (a) sarcomas and (b) endotheliomas, these latter outnumbering the sarcomas about four to one. (From what has been said before, the propriety of the term endothelioma can be judged.)

The case which aroused our interest in this subject occurred on the medical service of Dr. Herbert C. Moffitt in the University of California Hospital during the past winter. We wish to take this opportunity to express our thanks to Dr. Moffitt for the privilege of studying this case, and to Dr. Glanville Y. Rusk, associate professor of pathology in the University of California Medical School, for many helpful suggestions in the preparation of this study.

HISTORY OF CASE

Dr. R. C., a physician, 40 years of age, American, native of California, was admitted to the medical service of the University of California Hospital, Feb. 19, 1920. He died March 22, 1920. Patient was first under the care of Dr. George H. Evans at St. Luke's Hospital and the following notes were obtained from the history of that hospital. Patient was first seen Sept. 22, 1919, and gave the following history:

Complaint.—"Shortness of breath," and "pain in the left chest."

Family History.—Unimportant.

Past History.—In November, 1918, he had a rather mild attack of influenza which was followed by slight dyspnea. In May, 1919, he first noticed pain in

9. Schweninger: Ann. d. Krankh. z. München., 1878, p. 365.

10. Pallasse, E., and Roubier, C.: Les Tumeurs primitives de la Plèure, Ann. de méd., Par. **111**:243, 1915.

11. Bloch, M.: Néoplasms malins primitifs de la Plèure (Thésé de Par.), (Paris, Vigot freres), 1905, No. 414.

the left chest, and at the same time he began to lose weight and feel below par. June 11, 1919, he had his tonsils removed and the immediate effect of this seemed to be good as he gained weight and strength afterward. However, the pain in the chest continued and the dyspnea increased. In August, 1919, a diagnosis of pleurisy with effusion (left) was made, and the patient had a thoracentesis with the result of the removal of more than a liter of bloody

Fig. 1.—Roentgenogram (No. 14227, St. Luke's Hospital, Roentgen-Ray Department, Sept. 23, 1919) taken with the patient in the upright position.

fluid. Three days later thoracentesis was again performed and 28 ounces of bloody fluid was withdrawn. Sept. 22, 1919, the patient entered St. Luke's Hospital.

Physical Examination. — Nourishment fair. Pupils are unequal, the right pupil is larger than the left. The chest is asymmetrical; the left chest is flat and the left shoulder droops.

Roentgenoscopy of Chest: (Sept. 23, 1919.) The roentgenogram (Fig. 1) showed a grayness throughout the upper half of the left chest with a dense shadow at the left base which partially obscured the heart and diaphragm, although the heart was not displaced to the right. Interpretation of the plate left a doubt regarding the presence of fluid in the left pleura; while there was marked dulness at the left base, vocal fremitus and resonance were not entirely absent and no Grocco's triangle was present on the right side.
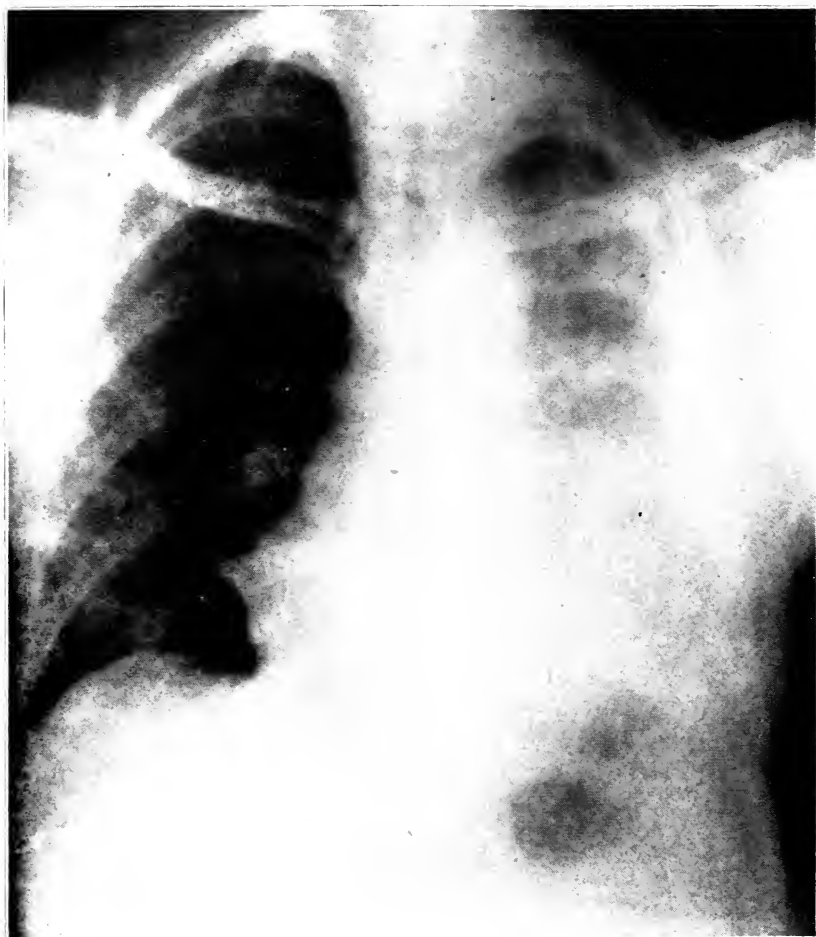
Fig. 2.—Roentgenogram (No. 14793, St. Luke's Hospital Roentgen-Ray Department, Dec. 30, 1919) taken with the patient in the upright position.

Blood examination: Hemoglobin, 95 per cent.; erythrocytes, 4,550,000; leukocytes, 8,000; polymorphonuclears, 72 per cent.; large lymphocytes, 28 per cent.; transitionals, 1 per cent.

Urine examination: entirely negative.

Patient continued to have considerable pain in the left lower chest. At this time he was afebrile, except following roentgen-ray exposure.

Oct. 8, 1919, the patient was allowed to return to his home at Hollister, Calif. He was forced to remain in bed after his return home and opiates were needed to relieve the pain in the left chest. About December 1, he was able to be up a few hours each day.

December 16, the patient was readmitted to St. Luke's Hospital.

Fig. 3.—Roentgenogram (No. 18161, University of California Hospital, Roentgen-Ray Department, March 6, 1920) taken with the patient in the prone position (anterior-posterior view).

Roentgenoscopy of Chest (Dec. 30, 1919): The roentgenogram (Fig. 2) shows great retraction of the chest on the left with what was apparently a thickened pleura at the left base.

The chest was tapped several times by Dr. Evans and bloody fluid was removed.

Jan. 24, 1920: At this time the patient began having periods when he was irrational. These periods increased until January 27 when he became very irrational, pulse rapid and weak.

March 2: The patient was transferred to the University of California Hospital.

Dr. Kerr's notes on admission: Thin, emaciated middle aged man, lying propped up in bed, face drawn, evidently in constant pain. The pain is periodical, located in the left chest and the left upper abdomen.
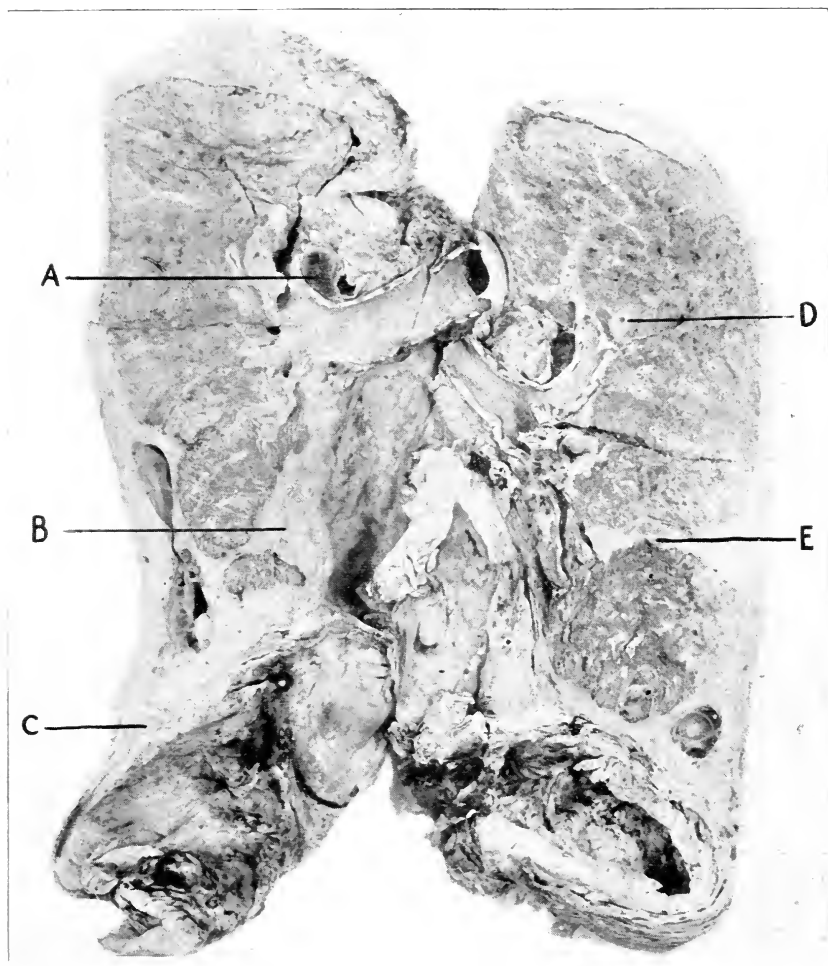
Fig. 4.—Photograph of cut surface of left lung showing the sheetlike thickening of the pleura, the enlarged glands at the hilus (a); thickening of pleura on mediastinal surface (b); remnants of diaphragmatic muscle (c); peribronchial tumor invasion (d); invasion of lung parenchyma by pleural tumor (e).

Pupils: Right is larger than the left; both are regular, and dilated, and react slightly. Fundi, negative

Chest: The left side of the chest is flattened and retracted. Excursion of the diaphragm is absent on the left, but present on the right. The percussion note over the right side is hyperresonant; it is flat on the left side from the

fifth rib in front downward, and from the angle of the scapula downward to the base on this side. Above this area of flatness in the left front there is an area of wooden tympany from the fourth rib upward to the clavicle. The breath sounds are bronchial in type in the upper part of the chest and distant to absent below, both anteriorly and posteriorly. No râles could be made out. No friction rub is palpable.

Heart: The right border is possibly displaced slightly to the left. The heart action is regular and rapid. The heart sounds are of poor quality. The pulses are equal, regular and of good volume.

Extremities: There is marked clubbing of the fingers. The left arm is definitely smaller than the right. Reflexes are equal on two sides and hyperactive throughout.

Sputum Examination: The sputum is very tenacious and of light lemon yellow. No odor or sulphur granules present. Preparation of fresh specimen shows great numbers of pus cells and many large phagocytic endothelial cells containing yellowish pigment. No Charcot-Leyden crystals or Curschmann's spirals were found. Stained specimens showed no bacteria, some cellular detritis with many pus cells and endothelial cells. No acid fast bacilli found.
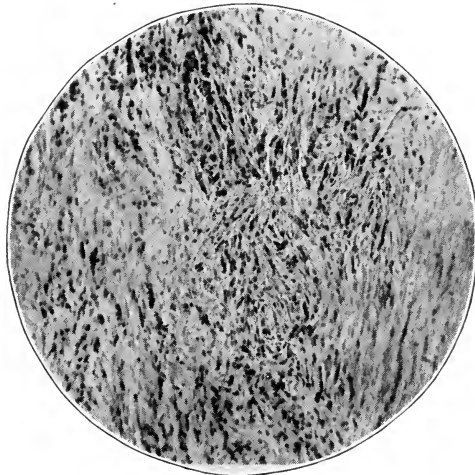
Fig. 5.—Section of the pleural tumor showing the diffuse type of growth (Objective 2, Ocular 4).

March 6: Patient complains of cramplike pains in the upper abdomen. The left abdominal wall is held rigidly. No masses can be made out by palpation or percussion.

March 8: Stool examination on five consecutive days has been negative. Urine examination: negative, except for slight trace of albumin.

Roentgenoscopy of Chest (March 6, 1920): "The plates (Fig. 3) look quite different now than the plates (Figs. 1 and 2) made at St. Luke's Hospital. The former plates I interpreted as pointing to an effusion with thickened pleura on the left, and although I looked carefully for evidence of malignancy in the neighborhood of the hilus, I was never sure that such a condition was present. Now it seems that one plate indicates quite definitely that a malignant process is present with a mass at the left hilus and displacement of the mediastinum toward the affected side." (Dr. Ruggles.)

March 9: Patient had diarrhea during the past week and today has some abdominal pain with some abdominal muscle spasm and distention.

March 10: Patient is drowsy. There has been an abrupt rise in temperature, pulse and respiration. During the past two days the patient had two roentgen-ray exposures of the chest, but these were very short exposures and probably of no marked therapeutic value.

March 12: Temperature, pulse and respiration continue elevated. There is a small area of dulness with bronchial breathing at the right base. Diarrhea continues.

March 13: Patient slightly better today.

Blood Examination: Erythrocytes, within normal limits; leukocytes, 17,600; polymorphonuclears, 82 per cent.; small lymphocytes, 6 per cent.; large lymphocytes, 8 percent.; endothelial cells, 2 per cent.; eosinophils, 1 per cent.; transitionals, 1 per cent.

Rectal Examination, March 16: High up and transversely situated, there is a firm, painless mass. The abdomen is held rigidly and an elongated, tender mass, 6 by 2 cm., can be palpated parallel to the descending colon at the brim of the pelvis.
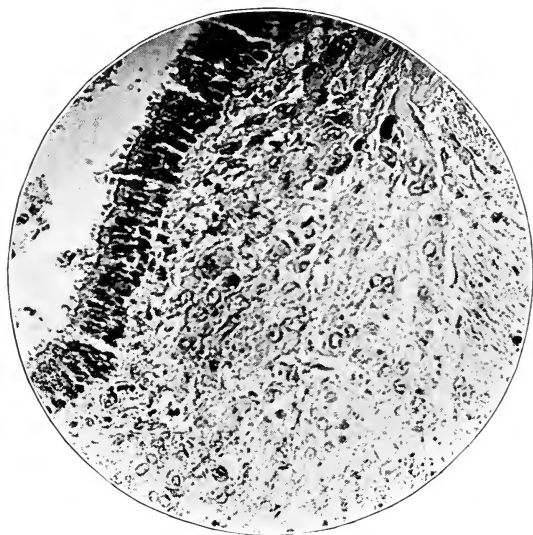
Fig. 6.—Section of a large bronchus, showing the extension of the growth along the submucosa (Objective 9, Ocular 4).

March 17: Condition practically unchanged.

March 18: Blood cultures: no growth in twenty-four hours, forty-eight hours, or six days.

March 22: Patient sank rapidly the last three or four days and died today.

Diagnosis: Final impression (recorded before postmortem).—Tumor of the left pleura with extension into the left lung and peritoneal cavity.

ABSTRACT OF NECROPSY (A. 20.50)

Anatomic Diagnosis: Primary tumor of the pleura, filling the left pleural cavity, invading the left lung and pericardium, and extending through the diaphragm with extensive invasion of omentum and multiple implantations over the peritoneum, also superficial invasion of spleen and liver. Multiple peritoneal adhesions with fibrinous plaques, associated with the adhesions in the pelvis. Adhesions of thickened omentum in left pelvis. Cloudy peritoneal

exudate. Marked atelectasis and edema of left lung. Moderate compensatory emphysema of right lung. Deformity of left chest. Misplacement of rectum (apparently congenital) to the left.

The body is that of an emaciated male adult of good stature. Rigor mortis is absent. Bodily heat is well retained. The left chest is diffusely sunken and the skin shows a blotchy hyperemia. At the usual site there is a well healed scar of an appendix operation. The pupils are circular, equal and moderately dilated. The sclerae are negative. The ears are negative. The fingers show moderate clubbing. The extremities are otherwise negative.

On making the usual median incision, the bodily fats are found to be deficient. The peritoneal cavity contains about 500 c.c. of turbid fluid which is without color. The omentum is greatly thickened, especially along its lower edge. It is drawn upward on the right side, but on the left side it is adherent by readily separable subacute adhesions to the cavity of the false pelvis and to the top of the bladder. The peritoneal cavity generally shows
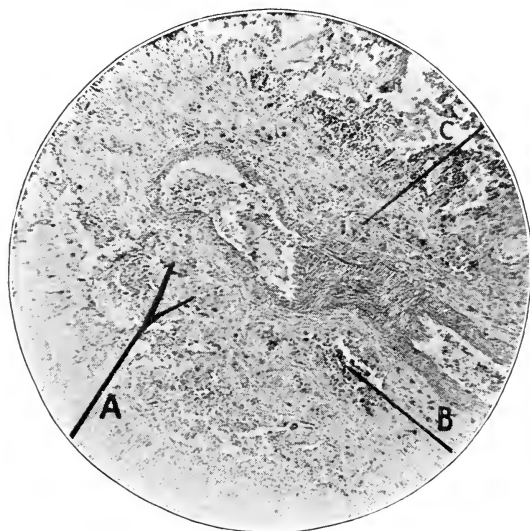
Fig. 7.—Section of lung parenchyma including a small vein showing the extension of the growth along the perivascular lymphatics (a, b and c) (Objective 3, Ocular 4).

a number of subacute readily separable adhesions on the upper and lower surface of the liver, in the convexity of the spleen, between the loops of small intestine and on the mesentery, also around the head of the cecum. In the pelvis the rectum is displaced to the left of the midline, and while there are adhesions about it they do not seem dense enough to have pulled the rectum over but it appears to be a congenital anomaly. At the site of the adhesions, especially those of the omentum where it is adherent to the bladder and on the surface of the loops of small intestine in the pelvis, there are a number of fibrinous flakes but unassociated with any hyperemia. The edge of the omentum is greatly thickened by an invading white, semitranslucent, cellular looking material, forming a cakelike mass, about 2 cm. thick by 5 cm. broad, near its adhesions in the left pelvis and becoming somewhat thinner as it extends upward across the abdomen. In the main mass of the omentum one sees similar implantations. The mesentery and peritoneal surfaces of the intestine show a number of tiny white implantations, some of

which are fairly well circumscribed and surrounded by a zone of hyperemia but others fade off at the edges and even show a tendency to infiltrate the surrounding tissue, and occasionally there is a slight puckering in the imme- diately adjacent tissue. Similar implantations occur in the pelvis and to a less degree on the parietal peritoneum.

The costal cartilages are unusually calcified for an individual of his age. The posteriar surface of the sternum shows diffuse adhesions on the left; there are none on the right. The right pleural cavity is free from adhesions, the left is entirely obliterated by dense chronic adhesions, on separating which the intercostal muscles show streaks of white fibrosis. The pericardial cavity shows a few readily separable subacute adhesions between the left side of the heart and the parietal pericardium over an area about 3 by 4 cm. The cavity also contains about 20 c.c. of serous transudate.

The heart is of normal size. The left ventricle is adherent, as noted above, to a somewhat roughened opaque area on the parietal pericardium, apparently due to an invasion of new growth from the overlying adherent pleura. The
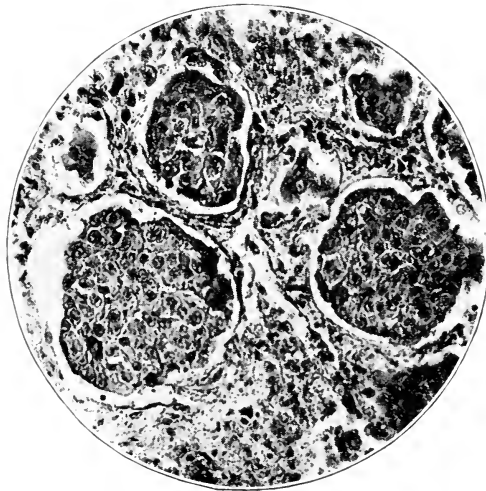
Fig. 8.—Section of lung parenchyma showing the masses of tumor cells to the alveolar spaces. Note the type of growth here (Objective 9, Ocular 4).

right side is somewhat full but not dilated. The endothelium of all the cham- bers including the valves is negative. The myocardium is of normal thickness, and slightly pale, but is otherwise negative. The first portion of the aorta shows a small amount of atheroma but is otherwise negative.

The right lung is moderately emphysematous, and shows the usual pigmen- tation. At the apex there is a slightly puckered scar surrounded by a narrow zone of parchment-like thickening of pleura. On section of the lower lobe there is a small calcified nodule about 2 mm. in diameter, apparently the remains of a tubercle. The lung is otherwise negative. The bronchi at the root are negative.

The left lung is removed with great difficulty on account of the universal dense adhesions. The organ appears to be about half its normal volume, and universally covered with a white fibrous layer which on section varies from about 2 to 5 mm. in thickness. Section through the lung shows the organ to be greatly compressed, and almost airless, except in the upper lobe. There is a moderate diffuse edema. The main bronchi were opened and no evidence of primary growth was seen. In the tissues just beneath the hilum and extend-

ing through to the pleura is an area which is relatively more firm, and contains a rather diffuse, though somewhat spotted, overgrowth of connective tissue. In this region as well as occasionally elsewhere in the lower lobe one sees a bronchus with definitely thickened walls due to a uniform white fibrous-looking tissue. The lymph nodes at the root show the usual pigmentation and some fibrous tissue invasion but nothing suggesting new growth. The thickened pleura likewise is so diffusely fibrous that one can make out no areas where the tissue appears more cellular as if from new growth. In the lower lateral angle of the lung the thickened pleura is separated into two leaves forming an irregular small cavity which contains a number of septa and about 15 c.c. of a clear straw-colored fluid.

The diaphragm on the left side was removed with the lung. It is composed of an opaque white tissue appearing somewhat more cellular than the pleura generally, also somewhat softer. Its under surface is greatly roughened and shaggy, and the spleen is adherent to it. On separating the latter there
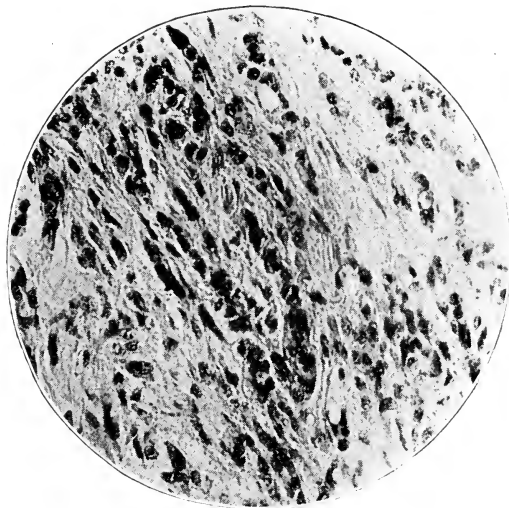
Fig. 9.—Section of omental tumor showing the diffuse type of growth (Objective 9, Ocular 4).

is noted an irregularly outlined layer of white semitranslucent material, apparently adherent new growth invading through the diaphragm.

The spleen is slightly reduced in size. On section it appears soft, and rather dark as if containing considerable blood. The malpighian bodies are small and indistinct and there is a moderate grade of fibrosis. At one point there is a deeply running scar about 1 cm. long by 2 cm. broad, connecting with the overlying new growth. This, however, somewhat resembles an old infarct.

The liver is slightly undersized. Superficially it shows a number of scattered, depressed, slightly scarred white areas which on section run a variable distance into the substance of the liver. The larger ones invade the liver parenchyma for a distance of 1.5 cm. Some of these are composed of fibrous tissue, others show areas suggesting necrosis and still others are markedly calcified. About each of these is a small amount of fibrosis. The gallbladder is deeply set in the liver. It appears negative, however, on section. The liver parenchyma shows a slightly mottled appearance due to a slight grade of passive congestion.

The suprarenals appear normal.

The kidneys are of normal size. The capsules strip normally. The fetal lobulations are slightly persistent. The surface is pale. On section the cortex is of normal thickness, and well differentiated from the medulla. The former is pale. The anatomical markings are regular. The kidneys are otherwise normal.

The pancreas is of normal size and negative on section.

The mesenteric and retroperitoneal lymph nodes are negative.

The mucosa of the gastro-intestinal tract is negative.

The aorta is normal.

The bladder, prostate, seminal vesicles and testes appear normal.

Microscopic Notes: *Pleural Tumor.*—The pleural surface is covered by a thickened sheetlike mass composed of a dense hyalin, rather acellular, connective tissue. All vestiges of the mesothelium of the two pleural surfaces have been obliterated. Along the costal margin of the thickened pleura there
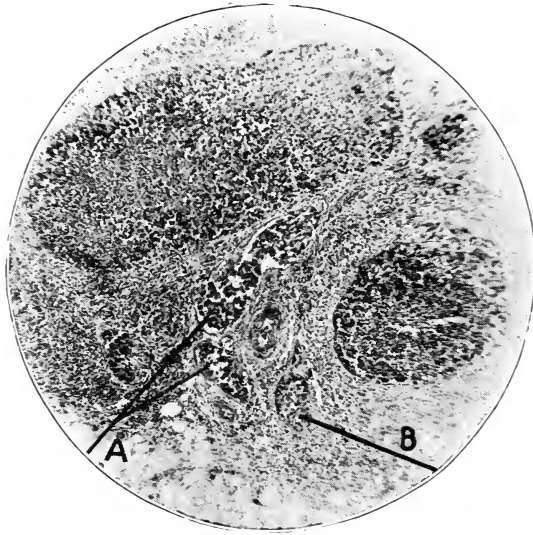
Fig. 10.—Section of mesenteric lymphoid nodule showing extension of tumor along the lymphatics (a and b) (Objective 3, Ocular 4).

is a rather diffuse distribution of tumor cells. Except in certain areas these cells are limited to a narrow zone along the surface. At certain points these cells extend more deeply into the thickened pleura, but at no point in the numerous sections examined do they become continuous with the nests of tumor cells along the inner zone of the thickened pleura adjacent to the lung. The morphology of the cells and the structure of the tumor are variable. The greater portion of the tumor shows a rather marked desmoplastic reaction with the tumor cells distributed rather diffusely throughout the fibrous tissue. In this diffuse type of growth the cells are elongated, have a homogenous acidophilic cytoplasm with an oval or elongated, hyperchromatic, moderately vesicular nucleus with one or more small faintly staining nucleoli. There are also numerous elongated multinucleated syncytial protoplasmic masses which show no intercellular differentiation. Mitotic figures are not numerous where the desmoplastic reaction is marked. There are also a few small nests of cells which occupy small lacunae in the connective tissue. None of these spaces have an endothelial lining. These cells resemble those described above, except

in general shape. They are spherical in shape, have a homogenous, deeply staining cytoplasm, with a round, hyperchromatic, moderately vesicular nucleus, with one or more small faintly staining nucleoli. Among these cell groups mitoses are more numerous. Along the inner zone of the thickened pleura adjacent to the lung parenchyma, the tumor cells occur in groups at intervals, but do not have the general distribution as noted along the costal margin. The variations in structure of the growth are the same. Many of the subpleural lymphatics are filled with tumor cells. These cells appear to have no relation to the endothelial cells lining the lymphatics. At many points the alveoli of the subpleural lung parenchyma are filled with masses of tumor cells, also an occasional small vein shows invasion. These cells are similar in every respect to those of the cell nests along the costal margin.

Lymph Glands of Hilus.—Sections of two enlarged lymph glands at the hilus of the lung show a rather diffuse tumor invasion. Many of the lymph spaces are distended with tumor cells. There are also large areas of diffuse tumor invasion with marked fibrosis.
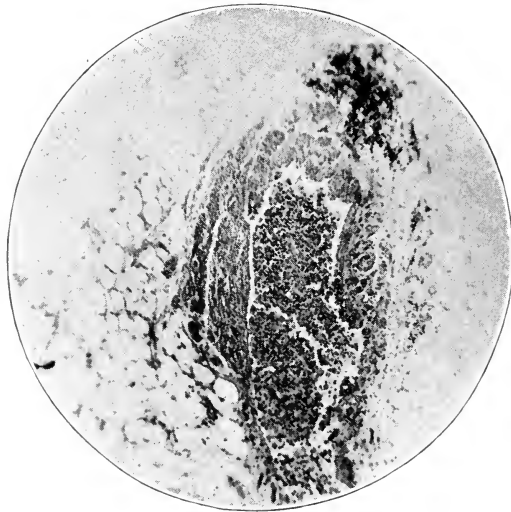
Fig. 11.—Same section as Figure 7, showing direct invasion of an adjacent vein (Objective 3, Ocular 4).

Bronchi.—Numerous sections taken from various portions of the bronchi show no evidence of involvement of the epithelium of the mucosa. Most of the bronchi show an extension of the tumor cells along the lymphatics of the submucosa. In some instances the cells extend along the finer lymphatics, approaching the epithelial lining of the mucosa. In some areas along the submucosa there is a marked desmoplastic reaction resulting in great thickening of the submucosa. There are also areas in which this desmoplastic type of growth has extended into the peribronchial tissues. There are numerous extensions of tumor cells into the alveolar spaces of the adjacent lung parenchyma.

Lung Parenchyma.—The subpleural lung parenchyma shows a compression atelectasis. The deeper lung parenchyma shows alternating areas of atelectasis and emphysema with a rather diffuse edema. There are several large areas of coagulative necrosis. In these areas the outlines of the alveolar spaces persist and are packed with large mononuclear polygonal cells. These areas represent areas of tumor invasion with necrosis. There are a few small foci of liquefaction in the areas of necrosis with an accumulation of poly-

morphonuclear leukocytes. In some areas the alveoli contain masses of fibrin but no cellular exudate. There is an occasional small bronchus which is filled with an exudate of polymorphonuclear leukocytes. Many of the lymphatics of the bronchioles and surrounding the blood vessels are distended with tumor cells. From these there are extensions of tumor cells into the adjacent alveolar spaces.

Diaphragmatic Surface of Pleura.—The tumor has invaded the diaphragm by direct extension, this extension being aided by invasion and extension along the lymphatic spaces. There are a number of lymph spaces which are distended with tumor cells. The growth here shows a marked desmoplastic reaction. In some of the sections the diaphragm persists as a few hyalinized fragments of skeletal muscle distributed throughout the growth.

Omental Tumor.—The omental nodules are similar in structure to the pleural growth. The growth here shows an active connective tissue reaction with tumor cells distributed diffusely throughout. The connective tissue stroma is

Fig. 12.—Section of liver showing the extension of tumor cells along the lymphatic (a); liver cells (b); (Objective 9, Ocular 4).

relatively less abundant and more cellular than in the pleural growth. There are numerous lymphatic spaces which are filled with tumor cells. Mitotic figures are also more numerous than in the pleural growth. The tumor cells present the same variation in morphology as elsewhere.

Mesenteric Lymph Nodes.—The lymph nodes in some instances are practically replaced by tumor cells. Many of the lymphatic spaces are distended with tumor cells. Some of the adjacent small veins show a direct invasion. The peritoneal implantations are small and superficial and do not invade the musculature of the intestine.

Spleen.—The spleen shows a marked diffuse passive congestion. The malpighian bodies are small and widely separated. At one point on the surface is a flat tumor mass, similar in structure to the omental tumor. At another point there is a bandlike projection of fibrous tissue into the splenic pulp. Through this dense fibrous stroma there are numerous tumor cells. An occasional mitotic figure is seen.

Liver.—There are numerous depressed areas on the surface of the liver. From these depressed areas there are bandlike projections into the liver parenchyma. These are composed of neoplastic tissue, similar to the omental growth, except that they are more scirrhus in type. At numerous points not far removed from the larger areas of tumor growth the interlobular lymphatics and veins are plugged with tumor cells. The adjacent liver lobules show no invasion. In the large tumor masses there are areas of hyalinization with calcification

The remainder of the viscera show no evidence of metastases nor anything of importance in relation to this case.

SUMMARY OF MICROSCOPIC PICTURE.—The cell type and manner of growth is variable, apparently dependent on surrounding environment. In those locations where the growth is apparently not hampered, the cells are of medium size, spherical in shape, have a homogenous eosinophilic cytoplasm, a relatively large round or oval, hyperchromatic, moderately vesicular nucleus, with small faintly staining nucleolus. This type of cell is found in the lymph nodes, lung parenchyma, and the extensions along the lymphatics. In these locations the cells tend to group together and assume a form of growth similar to epithelial growths. In those locations where the desmoplastic reaction is marked, the cells do not tend to group together but are diffusely disseminated throughout the connective tissue. The cell type in these areas is variable. There are numerous isolated cells similar to those described above. There are also numerous elongated or fusiform cells. These vary from those described above only in shape, the intracellular characteristics being the same. Some of these cells roughly resemble the young fibroblasts; however, they can be easily differentiated by their more chromatic nuclei and dense eosinophilic cytoplasm. There are also elongated multinucleated cytoplasmic masses which show no intercellular differentiation. It is evident that all of these cells are the same, with variations in shape and grouping, dependent on the surrounding environment of growth. It is also evident that the natural tendencies of these cells are to grow in an alveolar or medullary form. This is evidenced by the relatively larger number of mitotic figures in these areas.

POINT OF ORIGIN AND MODE OF EXTENSION.—In this case the growth is so far advanced that it is impossible to determine definitely the point of origin of the tumor, as the mesothelium of both the visceral and parietal pleura has been completely obliterated. Since the tumor cells are distributed rather diffusely over the costal surface of the thickened pleura and are separated from the inner zone adjacent to the lung by a layer of dense connective tissue, in which there are no tumor cells; and, furthermore, since the tumor cells occur only at widely separated intervals along the inner zone, one is influenced in drawing the conclusion that: the tumor probably arose at some point on the parietal pleura and extended secondarily to the visceral pleural surface, probably being favored by the inflammatory adhesions. Since the tumor does not possess the general characteristics of the endotheliomas derived from lymphatics and blood vessels, and is quite analogous in many respects to those tumors whose etiology has been traced to the lining mesothelium of the pleura (Benda[4] and Sprunt[5]), we feel justified in concluding that this tumor arose from the mesothelial lining of the pleura.

The mode of extension of the tumor is by continuity over contiguous surfaces, also by invasion and growth along the lymphatics. There are a few instances of direct invasion of the veins, but there is no evidence of a blood metastasis. The principal invasion of the lung is from the hilus along the bronchial and perivascular lymphatics. The invasion of the diaphragm is by direct extension, incidently invading and growing along the lymphatics.

MICROSCOPICAL DIAGNOSIS.—Although the mesothelial cells of the pleura have many of the characteristics of epithelial cells we do not see the justification of calling these tumors carcinomas. Likewise, since the mesothelial cells of

the pleura are usually regarded as being histologically and embryologically distinct from endothelial cells of the subpleural lymphatics and blood vessels, the term endotheliomas is not appropriate. We prefer to designate the tumor as a primary mesothelioma of the pleura.

OCCURRENCE

Glockner,[12] in 1897, collected forty-two primary malignant pleural tumors and added seven of his own. Bloch, in 1905, collected forty-seven cases of endothelioma and sixteen of sarcoma. Patterson[13] reported two of his own cases and collected ninety-six others; however, some of these could not be considered authentic because the data in regard to them was incomplete. The disease occurs more than twice as frequently in men than in women, and the greatest number of cases are found between the ages of 40 and 60. It appears to be a little more common on the right side than on the left, although it may be bilateral.

SYMPTOMS AND COURSE

The onset of pleural malignancy is usually insidious, and the course, once initiated, is progressive. Occasionally, the onset may be stormy with rapid development of the typical symptoms of an acute pleurisy. In the usual course the patient will be able to follow his business for some time, but he finds that he is losing energy, tires easily, and becomes dyspneic readily on the least exertion. Following this a dull, heavy, indefinite pain is noted in the chest. As a rule, there is little cough or expectoration, and the patient remains afebrile. Usually by the time the patient enters the hospital asthenia and cachexia are striking features. Paroxysmal attacks of dyspnea may occur and a state of "pseudoasphyxique generalement" (Bloch) becomes pronounced. The whole picture at this time strikes one as an advanced phthisis or myocardial disease in the terminal stage. The average duration of the disease from the onset of symptoms is from six to nine months.

PHYSICAL SIGNS

Immobilization, flattening and finally retraction of the affected side are the salient findings on inspection in pleural malignancy. Palpation may reveal enlarged glands in the neck or axillae, but they are not constant. The percussion signs indicate pleural effusion or thickened pleura which are not altered by pleural puncture and the removal of large amounts of fluid. The auscultatory findings point to the presence

12. Glockner, A.: Ueber den sogenannten Endothelkrebs der serosen Haute (Wagner-Schultz), Ztschr. f. Heilk. **18**:209, 1897.
13. Pattersen, H. S.: A Case of Endothelioma of the Pleura with a Review of Ninety-Six Cases, J. M. Soc. New Jersey **5**:373 (Jan.) 1909.

of a pleural exudate. In general there is nothing pathognomonic in the physical signs of this disease. The signs may vary as with the different types of pleurisy of other origins, depending on the amount of fluid present, the duration of its presence and finally the amount of thickening of the pleura. Nevertheless, fluid is present in some stage of the disease in practically every case (Bloch), and it is usually of the hemorrhagic type. It is notable that in some instances the first puncture will show a serous fluid which subsequently will become hemorrhagic or purulent. The amount of fluid is abundant and reforms rapidly after withdrawal. One of the most significant observations is relative to the temperature, which usually remains normal throughout the entire course of the disease. Exceptionally, there may be an evening elevation but this is usually found to be due to a superimposed pulmonary infection. Direct infection of the pleural fluid also occasions a rise in the temperature in certain instances. Accompanying the usual afebrile state the pulse likewise remains normal.

DIAGNOSIS

With all the refinements and possibilities of our modern diagnostic methods, primary neoplasm of the pleura cannot be diagnosed clinically with absolute certainty in all cases, although its presence can strongly be surmised in a fair proportion. It must be remembered that our clinical impressions, supplemented with the most careful laboratory methods, may indicate a neoplasm of the pleura only to find at necropsy that the primary growth is in the lung or elsewhere in the body.

The factors of most importance in the clinical diagnosis of this disease are composite rather than simple, and should, in the first place, take into consideration the symptoms and the special observations mentioned in regard to the history and physical signs; in other words, the clinical picture as a whole, as presented by the patient, is of great value. An individual with the signs of pleurisy with effusion in whom there is discovered a dark colored, hemorrhagic, pleural fluid (at times chocolate-like) which tends to increase rapidly after withdrawal and to become more hemorrhagic on subsequent withdrawal, should be regarded with suspicion as harboring an intrathoracic neoplasm. Add to this that symptomatically the withdrawal of the fluid affords little or no relief and at times increases the pleural pain, and that the physical signs are but slightly altered, if at all, by the drainage of the pleural cavity and other evidence of malignant intrathoracic disease is present.

The retraction of the chest wall, with obliteration of the intercostal spaces and the increased resistance met by the trocar in passing through

the pleura in performing the thoracentesis, are observations of some value, although not pathognomonic of pleural new growth since they may be noted also in tuberculous adhesive pleurisy. Small nodular implantation growths along the tract of the trocar puncture following thoracentesis have in rare instances afforded material for microscopic examination, as have fragments of tissue found on the point of the trocar on its removal. In doubtful cases which have baffled all the ordinary procedures and the diagnosis remains obscure, exploratory thoracotomy is helpful and justifiable. This procedure was done in Bayne-Jones' case.

ROENTGEN-RAY DIAGNOSIS

Unfortunately, the roentgen ray affords little help in determining the exact nature of the pleural disease in these cases. Barjon,[14] in his recent monograph on radiodiagnosis of pleuro-pulmonary affections, says: "Cancer of the pleura offers little of interest from the radiological point of view. It is seen most often under the form of pleurisy of the large cavity with effusion. Radioscopically it does not differ from ordinary pleurisy and it is for the clinician alone to prove its nature." Manges,[15] in a recent paper, confirms this statement and says that in his opinion pleural tumors in nearly all instances have massive effusions which constitute the only roentgen-ray findings.

CYTODIAGNOSIS

It is to Widal and Ravaut [16] that the credit of having first shown the importance of a careful histologic examination of the cell contents of pathologic effusions is due. As the result of their investigations, they stated their so-called cytologic formulae, which, in general, hold good in the majority of cases. Briefly, they are:

1. An excess of lymphocytes indicates a tuberculous process.

2. A preponderance of polymorphonuclear cells indicates an acute inflammatory process, frequently due to a pneumococcal or a streptococcus infection.

3. A passive or mechanical transudation contains, as a rule, a large number of endothelial cells, which often occur in groups ("placards"). (Besides the cardiac and renal transudates, malignant pulmonary and pleural disease are included in this group and present the same cytologic picture.)

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14. Barjon, F.: Radiodiagnosis of Pleuropulmonary Affections, New Haven, Yale University Press, 1918. (Translated by J. A. Honeij.)

15. Manges, M.: The Roentgen Ray in the Diagnosis of Pneumonia, Pleural Diseases and Pulmonary Tumors, New York M. J. **106**:917 (Nov. 17) 1917.

16. Widal, F., and Ravaut, P.: Compt. rend. Soc. de Biol. **52**:648, 1900.

It is the experience of numerous observers that in many cancerous pleurisies cancer cells are not found in the transudate, but in others they are present, and if identified seem to clinch the diagnosis. The recognition of cells of the different neoplasms is often very difficult, because some resemble lymphocytes, and others endothelial cells. Warthin [17] diagnosed sarcoma of the pleura by means of numerous spindle cells found in the pleural fluid obtained by aspiration and there are a few similar examples in the literature. It is of some importance to find cells in active mitosis in effusions. Warren,[18] in a study of the diagnostic value of mitotic figures in the cells of serous exudates, concludes that the presence of numerous cells undergoing mitotic division in serous exudates are almost diagnostic of malignant disease. These mitoses are more common in sarcoma than in carcinoma, the presence of a small number are of no significance, and in the majority of the effusions associated with malignant disease no division figures are seen in the cells.

Undoubtedly the early work in cytologic studies inspired too much optimism as to its ultimate value in the diagnosis of puzzling cases. The method offers a means which will usually exclude some inflammatory condition complicating a neoplasm, for here polymorphonuclear cells may predominate to such an extent as to lead to the conclusion that some acute infectious process is present overshadowing the associated malignant disease. We must conclude that cytodiagnosis is of a very limited value in the clinical diagnosis of malignant pleural disease.

CHEMISTRY OF PLEURAL EFFUSIONS IN THE DIAGNOSIS OF MALIGNANCY

Chemical studies of pleural effusions have not yielded a practical method for determining whether or not an effusion in a serous cavity is of malignant origin. The specific gravity and albumin content are of little value. Morris [19] studied the incoagulable nitrogen of puncture fluids with especial reference to cancer, and he came to the conclusion that a serous effusion with incoagulable nitrogen below 0.07 gm. per cent. is probably not of malignant origin. This increase of incoagulable nitrogen in certain carcinomatous fluids was thought to be due to the presence of proteolytic enzymes. It remains for the chemistry of

17. Warthin, A. S.: The Diagnosis of Primary Sarcoma of the Pleura from Cells Found in the Pleuritic Exudate, Med. News **71**:489, 1897.

18. Warren, L. F.: The Diagnostic Value of Mitotic Figures in the Cells of Serous Exudates, Arch. Int. Med. **8**:648 (Nov.) 1911.

19. Morris, R. S.: The Incoagulable Nitrogen of Puncture Fluids, with Special Reference to Cancer, Arch. Int. Med. **8**:457 (Sept.) 1911.

the future to supply us with a reliable test for the presence of malignancy, and judging by the progress of the past it does not seem improbable that this will be developed.

In the differential diagnosis several conditions must be taken into consideration. The most difficult and important disease to exclude in establishing a diagnosis of primary malignancy of the pleura is pulmonary tuberculosis in one of its diverse forms, and this, in truth, may not be possible even after a most painstaking study. The clinical history, physical examination, roentgen-ray findings, and a complete study of the pleural fluid, including its cytology, bacteriology and chemistry, may leave one in doubt, and in such a case certainty in diagnosis can be obtained only by an exploratory thoracotomy. Needless to say, such a procedure should not be adopted hurriedly, but it has its place today among the recognized diagnostic methods in obscure intrathoracic disease in which the other methods have failed.

Fortunately, in the majority of cases, if our clinical sense is alert and laboratory methods are utilized wisely, a correct diagnosis can be established.

The type of tuberculosis which may simulate a pleural neoplasm most closely is that which involves the pleura and lung almost simultaneously and is accompanied by a hemorrhagic pleural effusion. Although this is not a particularly common type of pulmonary tuberculosis, nevertheless, it is the most frequent condition which causes hemorrhagic pleural fluid. Besides malignancy of the pleura, lung and mediastinum, the other well recognized causes of hemorrhagic effusions include, traumatic and postoperative hemothorax, simple or idiopathic hemothorax, and the hemothorax which occasionally occurs in the course of chronic nephritis or cardiac disease. These last mentioned conditions are far less difficult to exclude in establishing the diagnosis of pleural malignancy.

Besides the application of these special methods to exclude tuberculosis, sedimented specimens of the pleural effusion should be examined in stained smears and by inoculation tests. The best results have been obtained by the use of comparatively large amounts of sedimented puncture fluid (from 40 to 50 c.c.) injected intraperitoneally into a guinea-pig. Continued negative results by this method are strong corroborative evidence against the presence of tuberculosis.

Following the exclusion of pulmonary tuberculosis, the next most difficult condition to differentiate from primary pleural new-growth is neoplastic disease of the lung, either of the primary or of the metastatic type. In the presence of a hemorrhagic pleural fluid with tuberculosis

excluded, a new growth of the lung should be considered more seriously than malignant pleural disease because the former occurs with far greater frequency. The special points that may prove of some value in differentiating primary pulmonary neoplasm from pleural malignancy are: (1) the early and persistent irritating cough encountered frequently in primary pulmonary tumors; (2), the typical currant jelly sputum and frequent hemoptysis; (3) finding the Lenhartz cell (Adler) in the sputum; (4), the absence of pain in some cases when seen early before the pleura has been involved (whereas pain is the most constant and distressing symptom from the onset in primary pleural tumors); and (5), the positive evidence afforded by the roentgen-ray study of the pulmonary neoplasm. Respiratory difficulties, cachexia, secondary anemia, an afebrile course, anisocoria, difference in the two pulses, clubbed fingers and variations in the cytologic picture and the chemistry of the pleural transudate may occur in both diseases and consequently are of no distinct aid in determining the exact point of origin of the disease process.

It is a well recognized fact that the symptoms and course of secondary lung tumors is quite distinct from the symptoms and course of primary pulmonary tumors (Adler). Such atypical and suggestive clinical pictures in intrathoracic disease should put one on guard, and a thorough search for the primary growth elsewhere should be instituted.

SUMMARY

We consider the cardinal points made in this paper to be as follows:

1. Primary, malignant, pleural tumor is a very rare condition.

2. These tumors constitute a distinct group and present a rather constant pathologic picture.

3. The definite point of origin of these neoplasms has not been determined absolutely.

4. We favor the mesothelial origin, and prefer to designate the tumor as mesothelioma rather than carcinoma, notwithstanding the fact that most of these neoplasms have been reported under the term endothelioma.

5. In the case presented above, the clinical diagnosis of malignant pleural disease was substantiated by the necropsy findings.

6. Pain in the chest is the earliest and most significant single symptom. It is usually severe and persistent in character and presents the most distressing feature of the disease.

7. The clinical course is of comparatively short duration and is usually afebrile.

8. There is nothing pathognomonic in the physical signs of the disease. A persistent, rapidly re-accumulating, hemorrhagic, pleural fluid is suggestive, and in its presence the possibility of pleural new growth should always be kept in mind.

9. The clinical picture studied as a whole offers the most valuable and trustworthy evidence.

10. The roentgen-ray examination fails to determine the exact nature and site of origin of the disease process in pleural malignancy.

11. Cytodiagnosis and the chemical study of the pleural transudates are of very limited value.

12. In those instances in which an exhaustive study has failed to establish a diagnosis, and pleural malignant disease is suspected, an exploratory thoracotomy is justifiable.

13. The two most important and at the same time difficult diseases to exclude in the differential diagnosis are pulmonary tuberculosis with hemorrhagic pleural effusion and primary malignant disease of the lung or bronchus.

FAT METABOLISM IN DIABETES MELLITUS *

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In the chemical investigation of diabetes in the past, interest centered chiefly about the question of disturbed carbohydrate metabolism, especially its attendant manifestations of glycosuria and hyperglycemia. Although the fact that in diabetes there is an impaired metabolism of fats as well as carbohydrates has long been recognized, the study of this phase of the problem, by accurate chemical methods, was begun only a few years ago. A simple procedure for the determination of lipoids in human blood was described by Bloor,[1] Joslin,[2] Joslin, Gray and Bloor [3] and Gray,[4] who pointed out the significance of an increased concentration of fat in diabetic blood.[5] Quite recently Brigham [6] emphasized the importance of controlling hyperlipoidemia in the treatment of diabetes. He says, "until the fact concentration of the blood is reduced no progress in increasing a sugar tolerance can be made." Analytical data bearing on this point are still meager and it seems desirable to add our observations to those already recorded in the literature.

We have made an analytical study of the sugar, fat and cholesterol in the blood in thirty-four cases of diabetes, noting the relationship of these substances to each other and to the diet.

PLAN OF INVESTIGATION AND METHODS

The subjects were patients in the diabetic unit of the department for the study of nutritional diseases of the Clifton Springs sanitarium. They included individuals of both sexes, varying in age from 8 to 73 years, and were in various stages of the disease. Chemical examination of the blood was made soon after admission, and the Allen-Joslin dietetic treatment for diabetes was begun immediately. Specimens of blood were thereafter analyzed for sugar, total lipoids [7] and whole

1. Bloor, W. R.: J. Biol. Chem. 17:377 1914; 26:417, 1916.
2. Joslin, E. P.: The Treatment of Diabetes Mellitus, Philadelphia and New York, 1917, p. 100.
3. Joslin, Bloor, Gray: J. A. M. A. 69:375 (Aug. 4) 1917.
4. Gray, H.: Boston M. & S. J. 178:16, 50, 91, 120, 156, 1918.
5. These authors also summarize the literature and give a bibliography of the most important publications on the subject.
6. Brigham, F. G.: Boston M. & S. J. 183:166, 1920.
7. By total lipoids we mean glycerids, phosphatids and cholesterol, as defined by Bloor, and determined as fatty acids.

blood and plasma cholesterol at frequent intervals, as indicated by the therapeutic needs of the patient. Blood for analysis was taken before breakfast, and on a diet of at least three days' duration. For the determination of blood sugar Benedict's [8] modification of the Lewis-Benedict method was used. Fat and cholesterol were estimated by the method of Bloor,[9] using the Kober instrument for nephelometric and colorimetric comparisons. The urine was examined daily by the usual methods. The results of the analyses and other important data regarding the patients are given in the accompanying tables and charts.

Of the cases studied, it is obvious that those that have been observed the longest period of time can give the most valuable information concerning the disease, both as regards its morbid physiology and its response to treatment. We have the records of thirty patients who have been treated for from two to six weeks and who have had their blood examined from two to eight times.

Keeping in mind the main object of this study, the metabolism of fat, we have attempted to group our cases according to the behavior of the blood lipoids in relation to the changes in the blood sugar level that occur as a result of dietary treatment. While such a classification must of necessity be somewhat arbitrary, it serves the purpose of convenience in studying the cases, and may facilitate comparison of clinical types. After the groups were arranged from purely laboratory data, they were compared from the standpoint of clinical history. There was found to be a resemblance in the previous history, chronicity, severity of disease and prognosis of the cases in the various groups so striking as to suggest true division into distinct types. The classification from laboratory data was made by one of us (N. F. B.) who was unacquainted with the clinical records, while the clinical classification was made independently by the co-worker, unbiased by the judgment on which the first grouping was based. The resemblances referred to will be discussed below.

GROUPING OF CASES

From the standpoint of laboratory findings, our cases seem to fall into the following groups:

(1) Blood fat increases steadily or intermittently, while sugar comes down.

(2) Blood fat parallels blood sugar.

(3) Blood fat stays at practically the same level while blood sugar decreases.

(4) Unclassified, because of insufficient data.

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8. Benedict, S. R.: J. Biol. Chem. **34**:203, 1918.
9. Bloor, W. R.: J. Biol. Chem. **24**:227, 1916; **31**:576, 1917.

TABLE 1.—ANALYSES OF CASES IN GROUP 1

No.	Age	Sex*	Date	Blood Analyses Sugar, per Cent.	Total Lipoids, per Cent.	Cholesterol Whole Blood, per Cent.	Cholesterol Plasma, per Cent.	Urine Sugar, Gm.	Urine Acetone	Diet Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Alcohol, C.c.	Calories	Weight, Lbs.	Remarks
3168	70	♀	3/19/20†	0.33	1.57	0.417	0.625	45	0	100	70	28	0	1,142	112	Chronic nephritis; edema preceded by arteriosclerosis
			3/27/20	0.21	2.0	0.476		0	0	29	12	6	5	283	107	
			4/3/20	0.18	1.2	0.475	0.756	0	0	58	30	25	5	637	105	
			4/13/20	0.20	0.66	0.476		0	0	70	50	30	5	850		
			4/21/20	0.18	1.28	0.330	0.476	0	0	60	50	30	0	850		
			4/24/20	0.17	1.0	0.250		Trace	0	60	50	30	0			
			6/8/20†	0.25	0.57	0.334	0.281	0	0				0			
			6/14/20	0.15	0.89	0.220			0				0			
2927	58	♂	2/11/20†	0.34	1.0	0.310		233	++						125	Severe long-standing case
			2/16/20	0.30	1.74	0.278		61	Trace	40	0	50	5	395	127	
			2/23/20	0.18	1.1			0	Trace	37	6	0	22	356	121	
			2/27/20	0.17	0.77			0	+	40	20	2	30	558	119	
			3/8/20	0.15	1.32			0	Trace	55	31	15	37	719	121	
			3/16/20	0.14	0.9			0	0	70		20	0	639	119	
3358	61	♂	4/6/20†	0.25	0.66	0.238		51	0						168	Severe case complicated by diffuse nephritis; obese at onset
			4/13/20	0.12	1.6	0.278	0.333	0	Trace	65	45	30	0	785	166	
			4/22/20	0.16	1.18	0.196	0.303	0	0	83	71	61	0	1,215		
			4/28/20	0.17	1.4	0.231	0.341	Trace	0	98	78	71	0	1,458		
1411	70	♂	3/8/20†	0.29	1.06			Trace		115	117	60	0	1,753	152	Severe long-standing arteriosclerosis, myocarditis and angina; received high fat diets before treatment
			3/19/20	0.23	1.46	0.238	0.294	0		92	100	86	0	1,612	198	
			3/26/20	0.21	1.2	0.231	0.264	0		90	100	75	0	1,560	196	
3984	62	♂	6/8/20†	0.42	0.74	0.394	0.508	80	++	18	0	0		156	109	Hereditary, greatly emaciated
			6/14/20	0.22	1.0	0.368	0.635	0	Faint trace							
			6/29/20	0.25	0.87	0.311		12	0	60	50	15	12	750		
1859	60	♂	3/1/20	0.20	0.72			0	0	60	68	68	0	1,124	300	Onset preceded by dose of thyroid extract, hypertension, myocarditis; obese
			3/8/20	0.15	1.1			0	0	63	72	88	0	1,232	298	
3661	71	♂	5/6/20	0.25	0.77	0.300	0.375	0	0	80	110	70	0	1,585	133	Arteriosclerosis; advanced case
			5/19/20	0.33	1.06	0.275	0.330	0	0	100	80	60	0	1,360	131	
4214	47	♂	5/10/20	0.20	0.90	0.166		Trace	0				0			Synovitis, chronic diffuse nephritis, obesity, ulcers of foot exaggerated by influenza
			5/29/20	0.15	1.2	0.187		Trace	+				0			
3645	60	♂	7/3/20	0.12	0.87	0.186		0	0	70	70	40	0	1,070		Hypertension, myocarditis, arteriosclerosis; alcoholic
			6/4/20	0.27	0.77	0.174	0.163	42	Very faint trace	70	70	40	0	1,070		
			6/17/20	0.21	1.02	0.178	0.261	0	Trace	51	41	60	0	815	199	
3925	64	♂	6/8/20	0.22	0.60	0.179	0.208	23	Trace		60	30	0	980		Necrosis of bone of foot, overweight; high fat diet previous to treatment
			6/12/20	0.15	0.91	0.180	0.256	0	0	65	80	70	0	1,336	158	
3985	54	♂	6/9/20	0.14	0.98	0.182	0.293	126	0				0		112	Hereditary type; arteriosclerosis, chronic diffuse nephritis, myocarditis and angina
			6/16/20	0.38	0.67	0.198	0.298	0		35	15	10	0	315	109	
			7/6/20	0.19	0.93	0.231	0.345	0		85	75	40	9	1,175	113	
				0.19	1.29	0.299	0.406	0	Trace							

* In this column, ♂ indicates male and ♀ female.   † On admission

Normal Values: Blood sugar, 0.09 to 0.12 per cent; total lipoids, 0.4 to 0.7 per cent; cholesterol, whole blood plasma, 0.160 to 250.

Group 1 (Table 1).—Especially interesting in this group are those cases which show a very marked increase of blood fat with a coincident drop in the blood sugar level at the time of the second blood analysis, soon after the initiation of the treatment. This is seen to a greater or less degree in all cases. After that the fat in some cases continues to rise; in others it falls, sometimes below the level shown in the first analysis. Later, through a series of fluctuations, it tends to return to the original value while the blood agar remains constant or
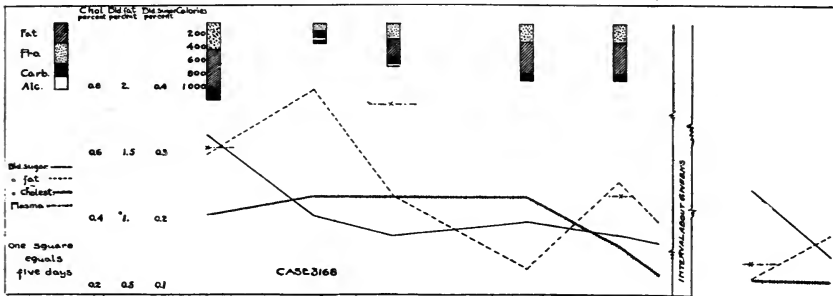
Fig. 1.—Showing behavior of blood lipoids in severe case of diabetes of Group 1. Observed about thirty-five days. Urine sugar on day of first blood analysis 45 gm. Graph on right of chart, readmission about six weeks later.
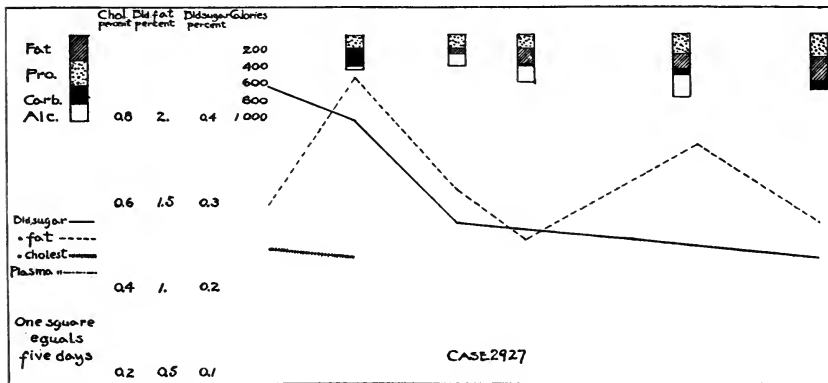
Fig. 2.—Group 1. Sugar in urine on admission 233 gm., blood lipoid value lowest at that time. As sugar excretion diminished lipoids in blood rose. Note absence of fat in diet at the time of most marked hyperlipoidemia.

shows a progressive decline. The cholesterol, both in whole blood and plasma, seems to rise and fall with the blood fat. Case 3168 (Table 1, Fig. 1) is typical of this condition.

The first rise of blood fat occurred during starvation or severe restriction of diet, and was probably due to the mobilization of stored up fat to supply the caloric needs of the body. It is well known

TABLE 2.—ANALYSES OF CASES IN GROUP 2

No.	Age	Sex*	Date	Blood: Sugar, per Cent.	Blood: Total Lipoids, per Cent.	Cholesterol: Whole Blood, per Cent.	Cholesterol: Plasma, per Cent.	Urine: Sugar, Gm.	Urine: Acetone	Diet: Protein, Gm.	Diet: Fat, Gm.	Diet: Carbohydrate, Gm.	Diet: Alcohol, C.c.	Diet: Calories	Weight, Lbs.	Remarks
2941	65	♂	2/13/20†	0.63	1.56	0.198	.....	56	0	...	...	...	0	.....	164	Necrosis of bone of left great toe; long standing mild case
			2/16/20	0.29	0.82	.....	.....	5	Trace	50	16	45	0	524	152	
			2/29/20	0.17	0.60	.....	.....	0	0	84	63	40	0	1,063	152	
			3/8/20	0.22	1.1	.....	.....	7.5	Faint trace	111	90	38	0	1,398	122	
			3/8/20	0.22	1.3	.....	.....	0	0	60	44	40	0	764	122	
3042	58	♀	4/3/20†	0.16	1.1	0.214	.....	0	Faint trace	...	...	...	0	.....	117	Long standing case; mild
			2/23/20	0.19	1.27	.....	.....	0	0	70	40	30	0	760	...	
3345	61	♀	3/8/20	0.15	0.83	.....	.....	0	Trace	70	50	30	0	850	...	
3726	46	♂	4/17/20	0.20	1.8	0.238	0.333	0	0	85	60	35	0	1,020	139	Hereditary; treated by high fat diet previous to admission
			5/13/20†	0.33	1.0	0.278	0.315	6	Trace	.....	.....	.....	0	.....	...	
			5/27/20	0.29	0.46	0.158	0.250	Trace	0	70	50	30	0	770	134	
			6/4/20	0.14	0.86	0.270	0.520	0.	Trace	95	90	70	0	1,470	134	
			6/12/20	0.18	1.1	0.288	0.407	0.	0	90	90	65	0	1,430	...	
			6/16/20†	0.21	0.93	0.299	0.440	7.5	Very faint trace	.....	.....	.....	0	.....	...	
1181	51	♂	2/16/20†	0.20	0.43	.....	.....	0	0	.....	.....	.....	0	.....	179	Hereditary; long standing, mild case
			2/23/20	0.27	0.94	.....	.....	0	0	70	80	40	0	1,160	176	
3223	55	♂	3/26/20	0.26	.....	0.195	0.278	7.5	0	.....	.....	.....	0	.....	205	Infected teeth; long standing mild case
			4/7/20	0.17	1.1	0.167	0.200	0	0	85	60	50	0	1,080	195	
			5/12/20†	0.16	0.77	0.204	0.238	0	0	95	75	55	0	1,278	...	
			5/15/20	0.17	0.78	0.214	0.242	0	0	95	75	55	0	1,278	...	
			5/19/20	.....	1.06	.....	0.312	0	.....	.....	.....	.....	0	.....	185	
2807	59	♀	1/22/20†	0.41	.....	.....	.....	96	++	.....	.....	.....	0	.....	87	Angina pectoris; severe case with low tolerance; (diet unreliable)
			2/13/20	0.25	1.1	0.221	.....	0	+ Faint trace	30	12	12	0	276	92	
			2/19/20	0.20	0.89	.....	.....	0	Faint trace	50	12	6	0	332	88	
			2/27/20	0.25	0.80	.....	.....	0	Very faint trace	60	20	10	0	460	...	
			3/19/20†	0.27	0.98	0.203	0.321	0	Very faint trace	86	9	8	0	237	84	
			7/10/20†	0.32	2.0	0.357	0.556	42	0	...	...	...	0	.....		

* In this column, ♂ indicates male and ♀ female.   † On admission   ‡ Figures for June 16, after meal.

that in fasting the blood lipoids may be increased; this, however, is not constant.[2] Gray[4] found the greatest increase after the second day of fasting, but his figures are not conclusive. Bang[10] was able to produce hyperlipoidemia in fasting dogs in good nutritional condition.

The sharp rise of the fat curve with a corresponding decline in the blood sugar incidental to the sudden withdrawal of carbohydrates from the diet, seems to bear out the suggestion of Joslin, Bloor and Gray[3] and of Bloor,[1] that the lack of these foods is an important element in the production of hyperlipoidemia. The rise seems to be most marked in cases in which the severest cut in carbohydrate allowance was made. The same conclusion with regard to the relationship of carbohydrates to lipoidemia has also been reached by Bang[10] from data obtained in fat feeding experiments on dogs. He found that dogs on a fat rich diet showed, almost invariably, an increase of fat in their blood, which could be prevented by a liberal supply of carbohydrates. He ascribed the appearance of abnormal amounts of fat in the blood to a diminished hepatic function attributable to the lack of sufficient carbohydrates in the circulating body fluids. He claimed that just as the presence of available carbohydrates facilitates the work of the liver in the deaminization of amino acids during protein metabolism, so do these foods increase the functional capacity of that organ to assimilate fats.

Although it appears probable that this rise in blood lipoids coincident with a fall in blood sugar is attributable to the effect of starvation, still it is not impossible that these results may show a metabolic relationship between fats and carbohydrates similar to the relationship which is known to exist between the metabolism of these two substances and the production of acetone bodies in starvation, forced fat feeding, and the acidosis of diabetic coma.

The depression of the fat curve below its initial level (Figs. 1 and 2) sometimes in spite of increased ingestion of fats, would suggest that the "fat pressure" resulting from the preceding increase was sufficient to cause a marked decrease in the blood lipoids by stimulating the fat burning mechanism to increased activity. Fatigue of this mechanism, however, soon sets in, as may be seen from the ensuing rise of the fat curve, even though the diet has not been changed. The source of fat in this second rise is apparently the ingested lipoids and not body fat. Case 2927 (Fig. 2) and Case 3168 (Fig. 1) illustrate this point. An excessive feeding of fat can produce high lipoid values in the blood.[1] In the series of cases presented here this is not shown, because the fat in the diet was controlled by the frequent analyses

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10. Bang, I.: Biochem Ztschr. **91**:104, 111, 1918.

TABLE 3.—ANALYSES OF CASES IN GROUP 3

No.	Age	Sex*	Date	Blood Analyses — Sugar, per Cent.	Blood Analyses — Total Lipoids, per Cent.	Blood Analyses — Cholesterol, Whole Blood, per Cent.	Blood Analyses — Cholesterol, Plasma, per Cent.	Urine — Sugar, Gm.	Urine — Acetone	Diet — Protein, Gm.	Diet — Fat, Gm.	Diet — Carbohydrate, Gm.	Diet — Alcohol, C.c.	Diet — Calories	Weight, Lbs.	Remarks
2926	61	♀	2/18/20†	0.34	1.15	.....	.....	19.8	0	..	..	..	0	.....	163	Preceded by active syphilis
			2/23/20	0.27	1.1	.....	.....	Faint trace	0	53	74	58	0	1,118	159	
535	12	♂	3/8/20	0.17	...	.....	.....	0	0	45	64	44	0	932	148	Onset when 8 years old; studies follow relapse caused by influenza
			3/19/20	0.20	1.20	0.172	0.198	0	0	46	59	48	0	907		
			3/27/20	0.15	1.2	0.185	0.209	0	Faint trace	71	67	58	0	1,119	57	
			3/30/20	0.33	1.4	0.245	.....	16	Faint trace	0	0	0	0	0		
2906	57	♂	4/13/20	0.16	1.3	0.256	0.416	0	Faint trace	50	30	20	0	570	56	Complicated by eczema
			3/1/20	0.14	0.72	.....	.....	0	—	95	85	75	0	1,445	173	
3863	53	♀	5/12/20	0.12	0.71	0.200	0.242	0	0	115	110	90	0	1,810	161	Constipation, obesity
			5/27/20†	0.33	0.66	0.250	0.348	27	0	..	..	..	0	.....	140	
			6/4/20	0.12	0.66	0.237	0.327	0	0	81	65	50	0	1,109	136	
			6/12/20	0.16	0.93	0.243	.....	77	0	75	75	60	0	1,215	135	
3317	66	♂	4/3/20†	0.39	...	0.256	.....	25	Trace	..	..	..	0	.....	187	Obesity
			4/6/20	0.22	0.90	0.204	0.278	0	—	48	12	29	0	416		
3270	21	♂	4/13/20	0.14	1.0	0.256	0.356	59	0	65	35	20	0	655	192	Preceded by influenza
			3/29/20†	0.33	1.5	0.270	0.556	0	0	50	20	16	0	516	114	
			4/7/20	0.15	1.3	0.258	.....	0	0	75	60	40	0	1,000	117	
			1/10/20	0.13	1.3	.....	0.250	Trace	0	63	65	127	0	1,045	114	
2694	48	♂	1/26/20	0.11	...	.....	0.250	0	Very faint trace	100	100	100		1,700	177	Preceded by acute infectious arthritis with necrosis of cartilage of sacro-iliac joint
3499	15	♀	5/13/20†	0.16	0.77	0.193	0.193	0	0	..	..	..	0	.....	76	Bronzed, anemic
			6/3/20†	0.14	0.77	0.196	0.417	Trace	0	28	3	5	0	159	75	
			4/22/20	0.18	1.1	0.278	0.469	0	0	56	28	30	0	610	74	
			5/3/20	0.13	1.1	0.273	0.375	0	0	74	45	35	0	481		
			5/10/20	0.12	1.2	0.288	.....	0	0	..	..	..	0	.....		

* In this column, ♂ indicates male and ♀ female.   † On admission

of the patient's blood. After the initial fat rise, further increases may indicate excessive ingestion of fat.

Gray [4] found that the lipoid values are higher in a negative than in a positive carbohydrate balance, and still higher in a zero balance. Our figures are not quite in accord with his conclusions, but rather show that in most cases the blood contains the least amount of fat at the time of marked glycosuria, and hence a most decided negative balance.

In addition to the cases that show the changes just discussed, there are some in which the plasma cholesterol behaves in a manner analogous to that of the total lipoids. Since an intimate relationship has been shown to exist between variations in cholesterol and the metabolism of fat,[3, 11] we believe that these cases illustrate the phenomenon
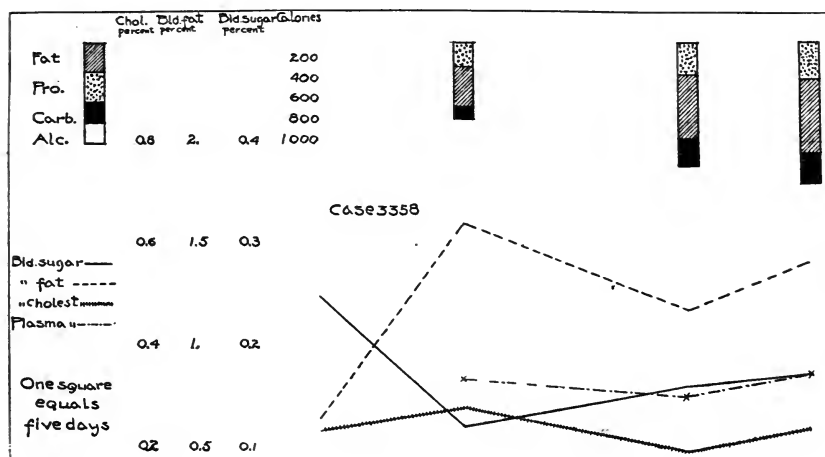
Fig. 3.—Group 1. Blood sugar dropped 50 per cent., while blood fat increased to almost three times its original value. Lipoids did not drop very low after first rise because of relatively high fat and low carbohydrate diet. Whole blood and plasma cholesterol vary with fats. Sugar in urine at the time of admission 51 gm.

of the response of increased lipoids during starvation or low carbohydrate intake. In several cases there is an increase of cholesterol which approximately parallels the increase in total lipoids.

The cases of this group present clinically histories of severe diabetes of long standing, complicated by nephritis, arteriosclerosis, and high blood pressure. They are all cases of true diabetes of low sugar tolerance, and some of the patients are rapidly losing weight. Two patients give a family history of diabetes, and three are obese persons. The prognosis is bad.

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11. Hueck, W., and Wacker, L.: Biochem. Ztschr. **100**:84, 1919.

Group 2 (Table 2).—In this group we include those cases in which fluctuations in the blood sugar level are accompanied by similar changes in the concentration of lipoids in the blood during the entire course of treatment. The number of cases that can be properly placed in this group is small, only eight out of twenty-six. It will be noted that, as a rule, the fat comes down more slowly than the blood sugar, while only a slight rise in the blood sugar is sometimes accompanied by a very marked increase in lipoids. Only in one or two instances did the fat fall to a normal level, while the blood sugar, though decreased, remained high. The return of the lipoid value to normal, along with a similar return of the blood sugar, is seen seldom, if ever.

The whole blood cholesterol varies but slightly and in some cases stays constant. The plasma cholesterol is high in most cases and does
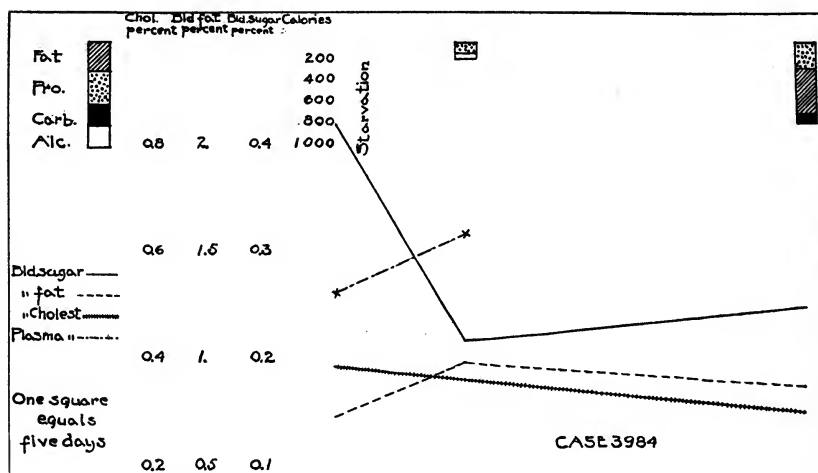
Fig. 4.—Group 1. Case shows lowest lipoid value during marked glycosuria (81 gm. in twenty-four hours) with no carbohydrate intake. Fat does not rise very high because of greatly emaciated condition of patient, and drops again when he reaches an almost zero carbohydrate balance. Plasma cholesterol high and increases markedly during starvation.

not seem to vary exactly with the total lipoids. Cases 2807 and 3223 do not seem to belong in this group. The critical fat determination on the admission specimen is lacking, and we feel that it would have shown that the cases belonged in Group 1.

Cases in Group 2, with the exception of Cases 2807 and 3223, are all characterized by a low grade of diabetes of a long standing. For the most part, the only symptom they exhibit is the frequent appearance of small amounts of sugar in the urine. The patients presented themselves for treatment after many years of neglect to remedy this condition. Most of them have a good sugar tolerance and do not

present a picture of such severe subjective illness as the cases in Group 1. Neither do they appear to get progressively worse as do the members of the first group.
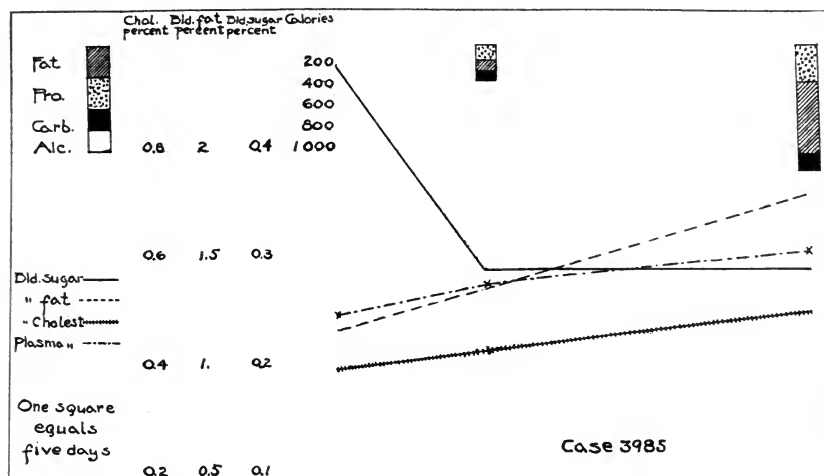
Fig. 5.—Group 1. Blood sugar decreases 50 per cent., maintains a steady high level, while blood fat increases progressively. Whole blood and plasma cholesterol closely parallel blood fat. Sugar in urine on admission 126 gm.
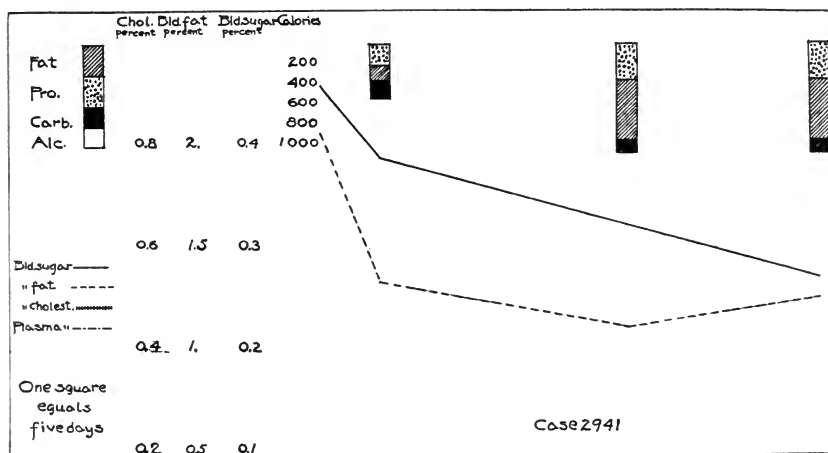
Fig. 6.—Group 2. Quite unlike cases in Group 1, blood fat shows at first an even more decided decrease than blood sugar. Urine sugar dropped from 56 to 5 gm. between first two blood analyses.

Group 3 (Table 3).—This group comprises about 26 per cent. (eight cases) of the cases studied. The fat shows practically no change with either blood or sugar diet. It is usually around 1 per cent.,

TABLE 4.—ANALYSES OF CASES IN GROUP 4

No.	Age	Sex*	Date	Blood Analyses — Sugar, per Cent.	Total Lipoids, per Cent.	Cholesterol — Whole Blood, per Cent.	Cholesterol — Plasma, per Cent.	Urine — Sugar, Gm.	Urine — Acetone	Diet — Protein, Gm.	Diet — Fat, Gm.	Diet — Carbohydrate, Gm.	Diet — Alcohol, C.c.	Calories	Weight, Lbs.	Remarks
858	18	♂	12/16/19	0.14	....	....	0.806	0	0	100	110	100	0	1,780	98	Hereditary type; bronzed icteric skin; diabetes preceded by excessive carbohydrate intake
			1/12/20	0.16	....	....	0.830	0	Trace	100	110	100	0	1,780	98	
			1/18/20	0.16	....	....	0.810	0	0	100	110	100	0	1,780		
			1/20/20	0.17	....	....	0.715	0	0	100	110	100	0	1,780		
			2/7/20	0.15	....	....	0.835	0	0	100	90	70	0	1,490	93	
			5/6/20†	0.15	1.35	0.750	1.100	0	0	100	90	70	0	1,490	95	
			6/3/20†	0.14	0.77	0.652	1.170	0	0				0		83	
2844	45	♀	1/6/20†	0.21	....	....	0.192	Trace	0	....	....	....	0	....	155	Chronic diffuse nephritis; obesity
			2/5/20	0.15	....	....	0.208	0	0	100	70	70	0	1,310	150	
			2/13/20	0.18	0.43	....	0.185	0	0	100	80	80	0	1,440	149	
2324	61	♂	12/2/19	0.40	....	....	0.250	41	Trace	....	....	....	0	....	186	
			12/12/19	0.14	....	....		0	Faint trace	90	80	67	0	1,420	134	
2886	58	♀	12/19/19	0.14	....	....	0.355	0	0	100	100	80	0	1,620	134	Ethmolditis
			2/6/20	0.13	....	....	0.228	Faint trace	0	68	72	180	0	1,352	154	
3634	57	♀	2/16/20	0.14	0.68	0.214	0.250	0	0	55	80	130	0	1,460	147	
4075	22	♀	5/10/20	0.14	1.1	0.190	0.217		0	80	60	50	0	1,060	150	
3874	68	♀	6/17/20†	0.32	0.72	0.174	0.226	24	....	....	....	....	0	....	99	Hypertension
1260	54	♂	5/13/20	0.17	0.89			Trace	0	....	....	....	0	....		Ulcer of leg
			5/23/20†	0.29	0.79	0.374	0.500	10	0	....	....	....	0	....		

* In this column, ♂ indicates male and ♀ female. † On admission

while the blood sugar drops rapidly or decreases progressively to a normal level. The whole blood cholesterol is remarkably constant. The plasma cholesterol is high in only two cases, and in one case it has the same value as that of the whole blood.

Clinically these cases are remarkable because of the fact that most of them gave a history of infection previous to the onset of glycosuria.
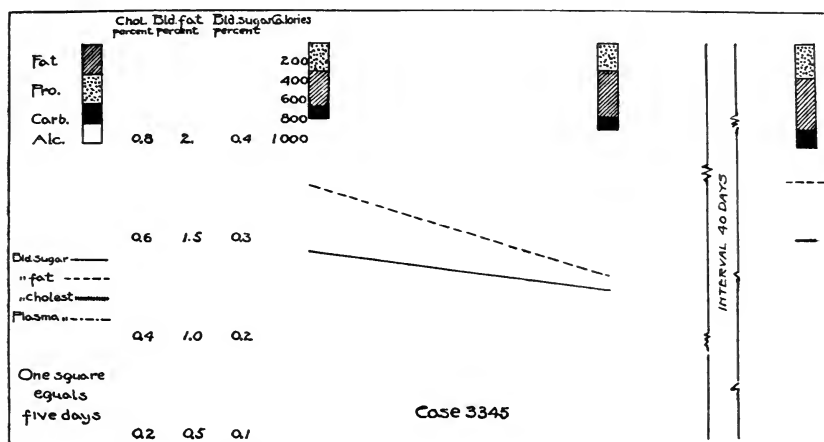
Fig. 7.—Group 2. Plotting of continuous curve of changes in blood constituents not possible because of long interval between last two analyses. Chart illustrates tendency in this patient for blood lipoids to vary with blood sugar.
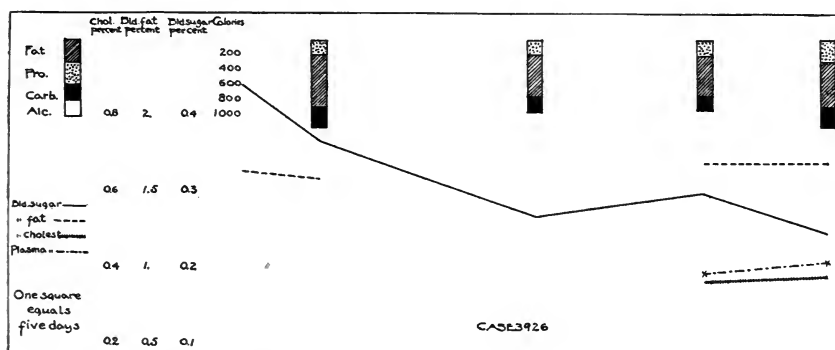
Fig. 8.—Group 3. A representative case of this group. Blood lipoids (four determinations) remain constant while sugar comes down. Sugar in urine on first day of treatment 19.8 gm.

This relationship is so marked as to suggest infection as an etiologic factor or a predisposing influence in these cases. The kinds of infections that figure in this connection are: influenza, syphilis, infection of joints and other infection of undetermined nature.

Group 4 (Table 4).—In the group of unclassified cases, we wish to call attention to Case 858. The patient is a young man, 18 years of age, who has been treated for diabetes for about three years. At first he built up a good tolerance, was getting on well, and his outlook as regards longevity was hopeful. Several months ago we noticed a very marked increase of his plasma cholesterol, which has stayed up ever since and has recently shown a further rise. Since this observation, the tolerance of the patient has gradually diminished, he has lost weight, and now looks bronzed and is very anemic. This case seems to illustrate the prognostic value of cholesterol determinations in diabetic blood.

SUMMARY AND CONCLUSIONS

Twenty-six cases of diabetes under treatment were compared in relation of the blood fat to the blood sugar and were found to fall roughly into three groups, the members of each group bearing certain clinical resemblances to each other.

About 42 per cent. of these cases showed, at the beginning of treatment, a marked increase of blood lipoids, along with a considerable drop of the blood sugar due to starvation or a severely restricted diet. This rise in the lipoid curve must not be taken as a measure of the degree of impairment of the fat burning mechanism; it may be due to a normal response to fasting and also to an insufficient carbohydrate intake. Clinically these were all severe cases of diabetes. Blood fats seemed to rise and fall with the blood sugar in almost 27 per cent. of the cases, decrease in the fat apparently progressing more slowly than the decrease in the blood sugar. All but two of these patients were in a milder stage of the disease. In about 31 per cent. of the cases there was an almost constant value for blood lipoids, at high level, while the blood sugar decreased. They all presented a history of infection previous to the onset of diabetes, and suffered from a somewhat more severe form of the disease than those of the preceding group.

The lipoid value seemed to be lowest in a negative carbohydrate balance, showing that the diabetic organism can utilize fats more readily in the presence of large amounts of sugar in the body, and that in "sugar free" patients there must be a great strain on the fat burning mechanism when large amounts of fats are fed. Evidence of this may often be seen in the high values for plasma cholesterol.

SOME VARIATIONS IN NORMAL BLOOD SUGAR *

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CHICAGO

I

INTRODUCTION

The effect of diet on the blood sugar of normal individuals was reported by Jacobson[1] in 1913 and by Strouse[2] in 1915. Bang's monograph[3] appeared in 1913 and contains a full discussion of blood sugar, both normal and pathologic. Since 1915, as a result of the perfection of chemical methods easily adaptable to the clinical laboratory, the study of blood sugar has become a clinical procedure. All methods in common use report results in grams per 100 c.c. of total blood or blood plasma; and a large collection of valuable data has resulted, especially in regard to diabetes mellitus and to other pathologic states.

Not a great deal of attention has been directed to normal variations, although present methods are so simple that studies of the same individual for a long period of time are easily performed. "Normal" values vary from 0.06 to 0.10 or 0.12 per cent., and it is generally accepted that the most important factor varying the normal is the food factor; carbohydrates having a definite effect on circulating blood sugar, protein and fat having no effect (Jacobson and Edwards[4]). Williams and Humphrey[5] studied thirty-nine young adults, for whom they found an average blood sugar of 0.11, with a range of 0.07 to 0.15. The examinations were made at intervals of from one to six hours after the previous meal, and as a group there was no well marked relationship between the time of eating and the blood sugar level. Apparently these investigators did not attempt to study the diurnal variations of the same individual. Epstein[6] published a long series of observations in which he attempted to prove that the percentage method of recording blood sugar was inaccurate. He believed that the actual amount of circulating blood sugar depended to a great

1. Jacobson, A. Th. B.: Biochem. Ztschr. **56**:471, 1913.

2. Strouse, S.; Stein, I. F., and Wiseley, A.: Johns Hopkins Hosp. Bull. **26**:211, 1915.

3. Bang, I.: Der Blutzucker, Wiesbaden, 1913.

4. Jacobson, A. Th. B., and Edwards, H.: Am. J. M. Sc. **159**:833, 1920.

5. Williams, J. R., and Humphreys, E. M.: Arch. Int. Med. **23**:537 (April) 1919.

6. Epstein, A. A.: Studies on Hyperglycemia in Relation to Glycosuria, New York, 1916.

extent on the blood volume, which he determined by the hematocrit method. Woodyatt [7] also is of the belief that "in interpreting blood sugar percentages there should be a correction for blood volume, or more exactly for the blood surface at the time of the blood sugar determination."

It would seem possible by a direct method of attack to learn something about normal variations as well as about the value of the percentage method of determining blood sugar. Epstein's criticism of the percentile method is based on the physiologic assumption that changes in blood volume occur after such things as diuresis, sweating, excessive intake of water, or catharsis. Woodyatt [7] could vary blood sugar in his injection experiments by varying the amount of water injected, although the development of glycosuria depended entirely on the velocity and the amount of sugar injected regardless of water intake. It would seem that if the physiologic stimuli which theoretically change blood volume are actually of importance in blood sugar determinations, it should be possible by varying such stimuli to change the blood volume and also the blood sugar percentage. Therefore, the addition of large amounts of water to the intake of a normal individual, or the elimination of water by profuse catharsis should be demonstrable in blood sugar readings, if such physiologic stimuli change the blood volume, and if such changes in the blood volume actually affect blood sugar percentage.

EXPERIMENTAL DATA

Five perfectly healthy young men and women were used as subjects. Blood was taken from each person at the same time each day: Subject 1, at 9 a. m.; Subject 2, at 9:15 a. m.; Subject 3, at 10:15 a. m.; Subject 4, at 11:15 a. m., and Subject 5, at noon. Breakfast for each person was the same daily, except when the nature of the experiment caused a change, which will be noted in the protocols. The breakfasts were as follows:

SUBJECT 1.—Miss B. One roll; 1 cup coffee with sugar.

SUBJECT 2.—Miss L. One piece toast; 1 glass milk.

SUBJECT 3.—Miss E. One piece toast; ½ cantaloupe or other fruit; 1 cup coffee.

SUBJECT 4.—J. K. One cup coffee; 1 glass water; 1 dish oatmeal.

SUBJECT 5.—S. One cup coffee; cream and sugar; fruit; cereal with cream and sugar; 1 egg; a piece toast.

Four of the subjects were workers in the laboratory, doing practically the same kind of work each day. The fifth subject was a

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7. Woodyatt, R. T.: Proc. Am. Soc. Clin. Investigation, 1919. (Reprinted from J. A. M. A. **73**:637 [Aug. 23] 1919.)

physician whose daily expenditure of energy was inconstant. By taking blood from each individual at the same time each day and by keeping breakfast constant, the food variation of the individual blood sugar is thereby controlled.

The Lewis-Benedict [8] method was used entirely. In earlier experiments many duplicate determinations were made, comparing the Lewis-Benedict with the modification of the Bertrand, first used by us (Strouse [2]) or with the original Folin-Wu [9] method. It was found that the Lewis-Benedict method gave the most constant and reliable results, and in this and subsequent work it has been the sole method employed. The same technician made all of the determinations. A slight modification in the method of obtaining the blood was adopted, which has simplified, without impairing the accuracy of the procedure. A carefully calibrated and standardized syringe of the tuberculin type was used to withdraw blood from an arm vein by means of a small hypodermic needle. Exactly 2 c.c. was obtained and immediately placed in a 25 c.c. volumetric flask containing distilled water and 3 per cent. sodium fluorid. The saturated picric acid was added and then the method was proceeded with as described by Lewis and Benedict.

EXPERIMENT 1.—July 21 and 22, 1919, the blood sugar of the five normal persons was estimated under constant conditions. July 23, Subject 3 took a large dose of magnesium citrate. July 24, Subject 1 added one glass of water to breakfast. Subjects 2 and 4 added three glasses of water. Subject 3 made no change. Subject 5 took no water, although for the preceding days he had drunk freely all through the morning. The results of this experiment are shown in Table 1.

TABLE 1.—BLOOD SUGAR DETERMINATIONS ON FIVE NORMAL PERSONS UNDER CERTAIN CONDITIONS

Subject	No.	Sex*	Age	Time, a. m.	Blood Sugar			
					July 21, 1919	July 22. 1919	July 23, 1919	July 24, 1919
T. B.	1	♀	23	9:00	0.08	0.095	0.07	0.07
L. L.	2	♀	23	9:15	0.084	0.084	0.068	0.065
H. E.	3	♀	27	10:15	0.088	0.085	0.066	0.057
J. K.	4	♂	38	11:00	0.081	0.078	0.056	0.063
S. S.	5	♂	37	12:00	.....	0.098	0.065	0.07
Average					0.083	0.088	0.064	0.065

* In this column ♂ indicates male, and ♀ female.

Study of the individual reaction shows that none of the efforts to change blood concentration have any effect on the blood sugar. It is possible, even probable, that changes in blood concentration resulting from such efforts would be evanescent and would have disappeared at the time the blood was taken,

8. Lewis, R. C., and Benedict, S. R.: J. Biol. Chem. **20**:61, 1915.
9. Folin and Wu: J. Biol. Chem. **38**:81, 1919.

just as the ingestion of 100 gm. of glucose by a normal person is demonstrable by increased blood sugar in one-half hour but no longer in an hour. All the figures show a fair uniformity for the first two days with a considerable drop of all on the third and fourth days of the experiment. This phase of the results will be discussed later.

EXPERIMENT 2.—Aug. 1 and 2, 1919. No particular attention was paid to any control factor, except the breakfast, which remained constant. As seen in Table 2, *all* of the individuals except Subject 3 show a considerable rise on the second day of the test, although nothing was done to produce such a rise.

TABLE 2.—BLOOD SUGAR DETERMINATIONS UNDER ORDINARY CONDITIONS

Subject	Blood Sugar	
	Aug. 1, 1919	Aug. 2, 1919
1	0.073	0.091
2	0.061	0.079
3	0.075	0.073
4	0.069	0.084
5	0.067	0.074
Average	0.069	0.08

EXPERIMENT 3.—March 4 and 5, 1920. In this experiment again variations in the individual curves occur, at this time the whole group dropping instead of rising as they did in the second experiment. Again no particular effort was made to change either the group or the individual blood sugar.

TABLE 3.—BLOOD SUGAR DETERMINATIONS UNDER ORDINARY CONDITIONS

Subject	Blood Sugar	
	March 4, 1920	March 5, 1920
1	0.110	0.087
2	0.092	0.072
3	0.10	0.070
4	0.125	0.10
5	0.099	0.096
Average	0.104	0.085

EXPERIMENT 4.—March 29 and 30, 1920. This experiment shows less individual and average variation than any of the preceding ones, but the protocol shows that March 29 Subject 5 had taken no water. March 30, Subject 1 took no water all morning. Subject 2 took 1 ounce of magnesium sulphate, with a profuse diarrhea up to the time of the test. Subject 3 made no change. Subject 4 took a full quart of water within the hour before the test. Subject 5 drank fully 2 quarts of water in the course of the morning up to the time of the test. Despite these rather strenuous efforts to change blood concentration, it will be seen that the only variation of any consequence is noted in Subject 3, who had made absolutely no change in her routine on the two days. The average on the second day is lower than the first, and each individual here, as in the preceding experiments, follows the average. Yet in this experiment, the possible changes in water concentration are decidedly greater than in previous experiments. Subjects 1 and 2 made efforts to diminish the water content of the blood; Subjects 4 and 5 made efforts to increase it; and these efforts are certainly in excess of those which might be expected in a normal routine. But these changes in blood volume, if they did occur, are certainly not demonstrable in the blood sugar percentage, which remained nearer a constant level than in previous experiments in which the subjects remained under more constant conditions.

TABLE 4.—Blood Sugar Determinations Under Special Conditions

Subject	Blood Sugar	
	March 29, 1920	March 30, 1920
1..	0.10	0.099
2..	0.08	0.075
3..	0.095	0.077
4..	0.087	0.077
5..	0.10	0.099
Average..	0.093	0.085

DISCUSSION

If blood volume can be changed by the procedures used in our experiments, and if the percentage of circulating blood sugar is affected by changes in blood volume, our experiments should demonstrate such changes. Our results clearly indicate that either the physiologic variations of the experiments are not sufficient to change the blood volume or that changes, if they occur, do not alter the percentage of circulating blood sugar. Surely the changes which might be expected to occur in daily life are usually less marked than those of our experiments, so that it seems justifiable to conclude that blood volume need not be considered a necessarily important factor in the usual clinical procedure of blood sugar determination. There is a wide difference between the slight and what may be called the acute changes studied and the chronic pathological disturbances of water balance associated with edema, marked anemia or the desiccation sometimes seen in advanced diabetics. In these pathologic disturbances of water balance the blood volume may, of course, be of importance for a more accurate method of determining blood sugar. Hiller and Mosenthal,[10] from a somewhat different point of attack, have shown that "spontaneous fluctuations in the amount of blood sugar as they occur in the diabetic individual are not paralleled by changes in the water content of the blood."

If, however, we combine the results of all our experiments in the form of a composite chart, plotting the daily blood sugar determinations for each individual as a continuous curve, and paralleling each curve by the average curve of all five individuals, we find some interesting data. It becomes apparent, first, that the average curve of all five persons from July, 1919, to March, 1920, is not a straight line, but it shows variations of from 0.064 to 0.104 per cent.—so-called normal extremes. Second, the average is higher in the cool month of March than in July and August. Third, each individual curve

10. Hiller, A., and Mosenthal, H. O.: J. Biol. Chem. **28**:197, 1916.
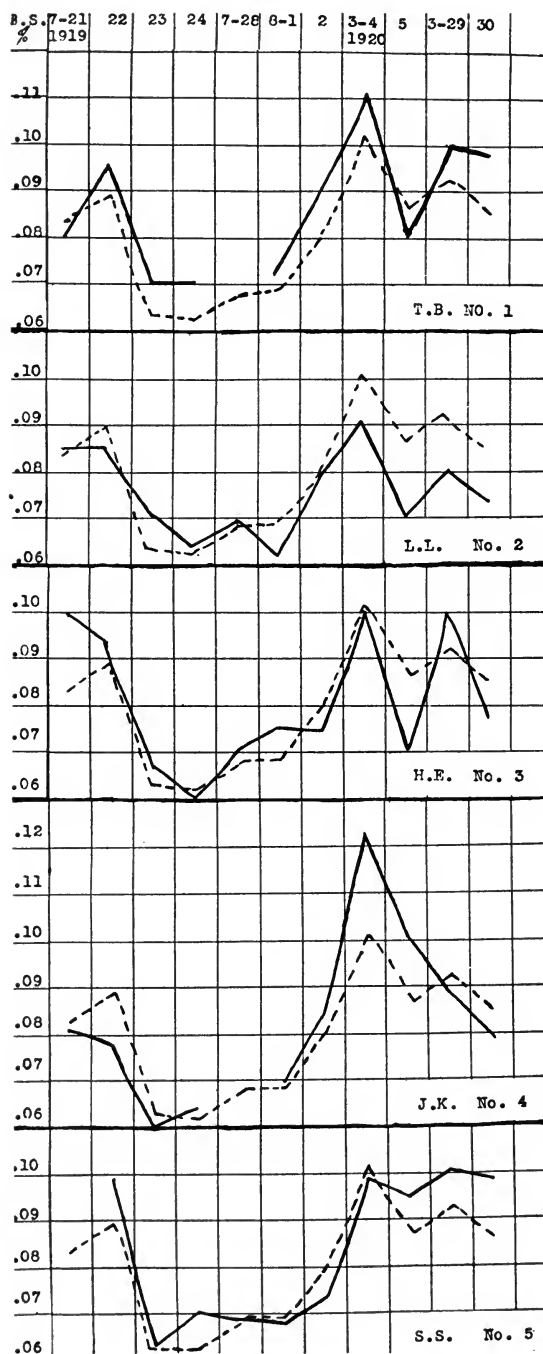
Each division represents the blood sugar curve of one normal individual (solid line), paralleled by the curve obtained by averaging all five normals (broken line).

follows the average. In other words, it is seen in studying the blood sugar of the same normal individuals from day to day that, generally speaking, when one changes, all change.

In attempting to explain these variations, we believe that the method of performing the experiments precludes the possibility that either a technical error or any of the control elements of the experiments might be responsible. All determinations were done by the same technician. If the varying controlled factors affected the blood sugar, they should not have done the same thing to all the subjects at the same time. If the protocol of Experiment 4 is studied, it is seen that there is no correlation between the control elements in the experiment and the result. The protocol of Experiment 1 shows that on July 21 and 22 all the blood sugars were higher than on July 23 and 24, and a similar thing is noted in all the other protocols, namely, that *all* are either higher or lower on the second day of the experiment. July 21 and 22 were bright, dry, cheerful days; July 23 and 24 were muggy, hot days, on which a normal person felt disinclined to do more than absolutely necessary work. July 23 and 24 were days on which any kind of effort was difficult as well as distasteful. Might not, then, the lowered blood sugar on these days indicate that there was a lessened expenditure of energy and a consequential lessened call on the energy supply? If there is such a lessened energy expenditure, the most readily available source of energy would probably be the first to show the effect, and the most available source of energy is found in carbohydrates. The changes in blood sugar, then, might be the result of weather influences. Bang [3] reviews the work that has been done on the effect of climatic conditions on blood sugar. Although most of this work has been performed on animals, the collected statistics seem to indicate that climatic conditions may affect the blood sugar. On the other hand, Dexter,[11] in his interesting discussion of weather influences, says that "varying meteorological conditions affect directly, though in different ways, the metabolism of life," and also that "the reserve energy capable of being used for intellectual processes and activities, other than those of the vital organs, is affected most by meteorological changes."

Graham Lusk,[12] discussing the regulation of body temperature, cites experiments proving a direct influence of surrounding temperature and humidity on metabolism, and concludes with the statement "the influence of climate is seen to be noteworthy."

11. Dexter, E. G.: Weather Influences, New York, 1904.
12. Lusk, G.: Science of Nutrition, Ed. 3, Philadelphia, W. B. Saunders Co., 1917, p. 151.

With the idea in mind that the changes in blood sugar found in our experiments might be the result of weather influences, we attempted to correlate our results with the weather reports. The temperature, humidity, direction and velocity of the wind were studied. We were unable to define any clear relationship between our charts and the weather maps. However, it is known (Dexter) that changes in an individual's reaction to weather conditions may either precede or follow actual changes in the weather. It was the feeling of our experiment subjects that on the days on which they felt more capable of working, the blood sugar readings were higher than on those days on which work was an effort. It is likewise apparent from the charts that the average blood sugar readings were higher in the cooler part of the year (March) than in July. Changes in water concentration resulting from perspiration should make the blood sugar readings higher on the hot days when perspiration is profuse, so that elimination of water through the skin need hardly be considered. Dexter cites instances [13] in which employers of labor do not allow their employees to undertake certain kinds of work when the weather conditions are not suitable.

In conclusion, we suggest, without being able to prove the correctness of the suggestion, that the delicate chemical balance of the body responds to slight stimuli just as readily as it does to greater stimuli. Under certain weather conditions, the body reacts by an unconscious or invisible increase in muscle movements with a resultant increase in energy expense. Under opposite weather conditions, muscle movements are lessened and there is a lessened energy expense. The variations which occur may be slight, but are probably met by variations in the supply of the most easily available source of energy. Carbohydrates are the most easily oxidizable source of energy, and the circulating blood sugar, representing, as it does, the sugar transportation system, may act as an indicator of these slight variations in energy expense.

CONCLUSIONS

1. Efforts to change blood sugar percentage of five normal persons by increased or diminished water intake and excretion failed to change the blood sugar percentage.

2. This indicates that for practical clinical purposes the blood sugar percentage method is accurate.

3. Daily variations of blood sugar percentage occurred in five normal persons. These variations seem to depend on changes in the weather.

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13. Dexter, E. G.: Weather Influences, New York, 1904, p. 239.

OBSERVATIONS ON ALIMENTARY HYPERGLYCEMIA *

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II

Uniformity of methods of procedure of the test for hyperglycemia after glucose ingestion has resulted in rather uniform conclusions regarding the test. Hopkins,[1] Hamman and Hirschman,[2] Janney and Isaacson,[3] Williams and Humphreys [4] showed that the normal individual usually reacted to a given dosage of glucose by a maximum rise in one-half hour and almost immediate drop after the half hour. The maximum rise rarely exceeded 0.16. Bailey [5] reports a normal alimentary glucose test in which the blood sugar in the whole blood was 0.172 in thirty-five minutes, 0.22 in one hour, and 0.216 in one hour and twenty-five minutes after the ingestion of 75 gm. of glucose. This type of curve is considered by most authors as distinctly abnormal, both in regard to the height which it reached and to the length of time it took before returning to normal. The diabetic curve is characterized by a rise at *any* time after the ingestion, a slow descent, and a height depending entirely on the grade of the reaction. There are, however, diabetic curves which closely simulate the normal. Williams and Humphreys,[4] for instance, present two charts (their Nos. 10 and 13) one of which is "practically normal," the other "suggests a very mild, indeed doubtful, diabetes." Yet one of these charts can be superimposed on the other. Hamman and Hirschman have suggested that the test indicated that diabetes represented a quantitative rather than a qualitative difference from the normal.

A review of our own work on this subject for the past few years has shown that there is a definitely normal and definitely pathologic type of reaction, but that between these two extremes the reaction may waver either way. The investigation here reported concerns mainly the interpretation of the wavering type of reaction, its relationship to clinical diagnosis, and its value in the study of the metabolic change in diabetes.

The question as to the blood sugar level at which glycosuria appears, the so-called renal threshold, is one, I believe, which involves consider-

1. Hopkins, H. H.: Am. J. M. Sc. **149**:254, 1915.
2. Hamman, L., and Hirschman, I. I.: Arch. Int. Med. **20**:761 (Dec.) 1917.
3. Janney, N. W., and Isaacson, V. I.: J. A. M. A. **70**:1131 (April 20) 1918.
4. Williams, J. R., and Humphreys, E. M.: Arch. Int. Med. **23**:537 (May) 1919.
5. Bailey, C. V.: Arch. Int. Med. **23**:455 (April) 1918.

ably more than the metabolism or mobilization of sugar. The retention by the blood of other metabolic products, the concentration of such products in the blood, the ability of the kidney to excrete, should be considered when discussing the renal threshold for sugar. This phase of the problem is now receiving study, and discussion of it will therefore be deferred.

THE NORMAL REACTION

The usual technic was employed. One hundred gm. glucose in 300 c.c. lemonade was given at about 8 a. m. on a fasting stomach. Blood sugar was studied by the Lewis-Benedict method [6] just before the ingestion of the glucose, and usually at intervals of 30, 60, 120 and 180 minutes after the dose. The urine was tested synchronously with the blood sugar, and when present in the test is charted in grams per cent. and grams per hour for the period examined. We tested eight normal persons and found the two characteristics of the normal curve to be (1) it reaches its height in one-half hour and descends immediately; (2) the height is not above 0.145 and in our cases averaged 0.108 per cent. The results of all normal tests are shown in Table 1.

TABLE 1.—NORMAL BLOOD SUGAR REACTION AFTER 100 GM. GLUCOSE

Name	Starvation	½ Hour	1 Hour	2 Hours	3 Hours
A.*	....	0.06	0.06	0.06	0.08
H.	0.083	0.083	0.068	0.055	0.052
B.*	0.060	0.07	0.07	0.05	0.057
L. B.	0.073	0.115	0.083	0.078	0.067
L. D.	0.052	0.11	0.073	0.064	0.073
S. K.	0.090	0.143	0.133	0.117	0.116
F. B.	0.077	0.142	0.133	0.125	.....
O. S.	0.095	0.142	0.125	0.111	0.111
Average	0.076	0.108	0.093	0.083	0.078

* Tests were performed with the Kowarsky method (Strouse) which usually read lower than the Lewis-Benedict method.

DIABETES

As has already been extensively shown, the blood sugar level after the ingestion of glucose by the diabetic may reach almost any height at any time after the ingestion and is very likely to remain high for a considerable period. In contrast to the normal the characteristics of the typical diabetic curve are: (1), height is rarely reached in the first half hour, but usually occurs at the hour or later and descends slowly; (2), it may reach any height. Table 2 shows data of a representative of the severe diabetic type.

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6. Strouse, S.: Arch. Int. Med. **26**:751 (Dec.) 1920.

TABLE 2.—Typical Diabetic Curve of Mrs. G., a Diabetic of Many Years' Standing

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar, Gm. per Hour	Urine Quantity, C.c.
8:05 a.m.	0.11	0	0	100
8:10 a.m. (50 gm. glucose)				
8:40 a.m.	0.15	0	0	70
9:10 a.m.	0.24	0.4	1.76	220
9:40 a.m.	0.20	0.8	1.92	122
10:10 a.m.	0.20	1.5	2.40	80

In this table it is seen that the height reached in one hour is above 0.145, there is a continued hyperglycemia and the descent does not even start in two hours. A type between the normal and the extreme diabetic was Mr. L., aged 50, of a diabetic family, who himself had occasionally shown traces of sugar but had no symptoms of diabetes (Table 3).

TABLE 3.—Data of G. L.

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar, Gm. per Hour	Urine Quantity, C.c.
8:25 a.m.	0.09	0	0	
8:30 a.m. (100 gm. glucose)				
9:00 a.m.	0.105	0	0	17
9:30 a.m.	0.15	1.35	0.459	17
10:30 a.m.	0.13	5.4	3.35	62
11:30 a.m.	0.10	3.0	1.44	48

Table 3 shows its height in the hour and yet it reaches only 0.15. The large amount of glucose excreted, his reaction in daily life to increased carbohydrate intake as well as his family history all point to his having a true diabetes mellitus. Yet the only difference between this patient and the normal is shown by the curve reaching its height in an hour and by the considerable glycosuria. An even milder diabetic is Mr. S., (Table 4), who at the time of the test was sugar free, but who could produce glycosuria at will by dietary indiscretion.

TABLE 4.—Data of Mr. S.

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar, Gm. per Hour	Urine Quantity, C.c.
8:10 a.m.	0.08	0	0	
8:15 a.m. (50 gm. glucose)				
8:45 a.m.	0.14	0	0	15
9:15 a.m.	0.12	0	0	15
9:45 a.m.	0.10	0	0	13

Although this man was and still is definitely diabetic, his reaction at this particular time to 50 gm. glucose is in no way distinguishable from the normal reaction to 100 gm.

In states of hyperthyroidism I have curves identical with the diabetic and with the normal (Tables 5 and 6).

TABLE 5.—H. S., Sugar Curve in Hyperthyroidism

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar, Gm. per Hour	Urine Quantity, C.c.
7:55 a.m.	0.095	0	0	250
8:00 a.m. (100 gm. glucose)				
8:30 a.m.	0.17	0	0	0
9:00 a.m.	0.22	1.8	0.81	45
10:00 a.m.	0.20	2.2	1.54	70
11:00 a.m.	0.18	3.0	0.24	8

TABLE 6.—F. B., Sugar Curve in Mild Hyperthyroidism

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar, Gm. per Hour	Urine Quantity, C.c.
8:35 a.m.	0.077	0	0	21
8:40 a.m. (100 gm. glucose)				
9:20 a.m.	0.142	0	0	0
9:50 a.m.	0.133	0	0	26
10:50 a.m.	0.13	Faint reduction	0.51	45

TABLE 7.—S. R., Sugar Curve in Cirrhosis of Liver (Syphilis)

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar, Gm. per Hour	Urine Quantity, C.c.
7:25 a.m.	0.128	0	0	58
7:30 a.m. (100 gm. glucose)				
8:00 a.m.	0.148	0	0	40
8:30 a.m.	0.22	0	0	33
9:30 a.m.	0.308	1.44	1.37	95
10:30 a.m.	0.275	1.22	0.61	50

The curves in cases of cirrhosis of the liver (Table 7), pituitary disease (Table 8), thromboangiitis obliterans (Table 9) and even chronic nephritis (Table 8) are *as far as their blood sugar is concerned* identical with those found for the diabetic.

TABLE 8.—B. R., Sugar Curve in Pituitary Disease and Nephritis

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar, Gm. per Hour	Urine Quantity, C.c.
7:50 a.m.	0.081	0	0	95
8:00 a.m. (100 gm. glucose)				
8:30 a.m.	0.169	0	0	18
9:00 a.m.	0.183	0	0	21
10:00 a.m.	0.22	0	0	16
11:00 a.m.	0.22	0	0	36

Rohdenburg, Bernhard and Krehbiel [7] originally thought they had found a specific reaction in cancer patients, but in a recent study [8] of many miscellaneous conditions they report that many absolutely similar curves are found in conditions "as widely different as diabetes mellitus, tuberculosis, epithelioma and pregnancy."

TABLE 9.—H. G., Sugar Curve in Thromboangiitis Obliterans

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar, Gm. per Hour	Urine Quantity, C.c.
8:30 a.m.	0.111	0	0	0
8:35 a.a.m (100 gm. glucose				
9:05 a.m.	0.181	0	0	46
9:35 a.m.	0.20	0	0	26
10:35 a.m.	0.192	0	0	128
11:35 a.m.	0.111	0	0	90

Whatever the fundamental significance of alimentary hyperglycemia may be, results of the test indicate that the reaction is definitely non specific. The diabetic patient rendered "normal" by treatment may react to 50 or 100 gm. of glucose in exactly the same way as the normal person. Also, other diseases, such as cirrhosis of the liver exophthalmic goiter, chronic arthritis (Pemberton [9]) give "diabetic curves." This lack of specificity between normal and diabetic individuals is quantitative rather than qualitative, at least in regard to sugar mobilization. This suggestion was made by Hamman and Hirschman.[2] Woodyatt,[10] in discussing acidosis in diabetes, says that "the difference between a total diabetic, so-called, and a healthy person is purely relative." If, then, the difference is merely quantitative, it should be possible to feed enough glucose to normal individuals to reproduce at will either the mild or the severe type of diabetic curve. Taylor and Hulton [11] fed 200, 300 and 400 gm. of glucose to normal persons at 10 a. m., after breakfast, and took the blood three hours later. They were unable to show a hyperglycemia at this time, and only an occasional glycosuria. However, by performing the test as outlined, I have been able to vary the reaction of normal persons simply by changing the amount of ingested glucose.

7. Rohdenburg, G. L.; Bernhard, A., and Krehbiel, O.: J. A. M. A. **72**:1528 (May 24) 1919.

8. Rohdenburg, G. L.; Bernhard, A., and Krehbiel, L.: Am. J. M. Sc. **160**: 577, 1920.

9. Pemberton, R., and Foster, G. L.: Arch. Int. Med. **25**:243 (Feb.) 1920.

10. Woodyatt, R. T.: J. A. M. A. **66**:1910 (June 17) 1916.

11. Taylor, A. E., and Hulton, F.: J. Biol. Chem. **25**:173, 1916.

TABLE 10.—Sugar Curve of Mr. M., July 7, 1920

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, Gm. per Cent.
8:10 a.m.	0.10	0
8:15 a.m. (150 gm. glucose)		
8:45 a.m.	0.12	0
9:15 a.m.	0.125	0
10:15 a.m.	0.105	0
11:15 a.m.	0.10	0

The same person, July 9, 1920, received 200 gm. of glucose.

TABLE 11.—Sugar Curve of Mr. M. After Ingesting Glucose July 9, 1920

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.
9:05 a.m.	0.111	0
9:10 a.m. (200 gm. glucose)		
9:40 a.m.	0.143	0
10:10 a.m.	0.154	0
11:10 a.m.	0.119	0
12:10 p.m.	0.10	

His reaction to 200 gm. glucose could be superimposed on Table 3, that of the mild diabetic. With 150 gm. of glucose the reaction is perfectly normal. With 200 gm. it is also normal, except that the height of the curve is reached in one hour and it is slightly above the normal values as we have found them.

Another man, Mr. J., apparently in good health, received 200 gm. glucose July 10, 1920, with the following results:

TABLE 12.—Sugar Curve of Mr. J. After Ingesting Glucose

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Quantity Urine, C.c.
8:00 a.m.	0.11	0	0
8:05 a.m. (200 gm. glucose)			
8:35 a.m.	0.20	Trace	115
9:05 a.m.	0.245	Trace	
10:05 a.m.	0.156	Trace	35
11:05 a.m.	0.133	Trace	50

This reaction is definitely diabetic in type, reaching its height in an hour and showing considerable hyperglycemia and very slight glycosuria without a return to the starvation level at the end of three hours.

Another illustration of the lack of type differentiation is seen in the case of Dr. X., who at the time of observation had a boil on the back of his neck. It had been pointed out before (among others by Becker[12] and Strouse[13]) that both furunculosis and carbunculosis are often associated with disturbances of carbohydrate metabolism.

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12. Becker: München. med. Wchnschr. **58**:2064, 1911.
13. Strouse, S.: Johns Hopkins Hosp. Bull. **26**:214, 1915.

This subject is a physician who had repeatedly examined his urine for sugar but had never found it present. July 8, 1920, he was given 100 gm. of glucose.

TABLE 13.—SUGAR CURVE OF DR. X

Time	Blood Sugar, Gm. per Cent.	Sugar in Urine	Quantity Urine, C.c.
9:00 a.m.	0.095	....	0
9:10 a.m. (100 gm. glucose)			
9:40 a.m.	0.143	Trace	100
10:10 a.m.	0.125	Trace	25
11:10 a.m.	0.111	Trace	140
12:10 p.m.	0.111	Trace	45

July 12, 1920, he received 150 gm. glucose in 300 c.c. lemonade.

TABLE 14.—SUGAR CURVE OF DR. X. AFTER INGESTING GLUCOSE

Time	Blood Sugar, Gm. per Cent.	Sugar in Urine	Quantity Urine, C.c.
9:00 a.m.	0.10	None	55
9:10 a.m. (150 gm. glucose)			
9:40 a.m.	0.175	Trace	17
10:10 a.m.	0.188	Trace	55
11:10 a.m.	0.125	Trace plus	85
12:10 p.m.	0.111	Trace plus	23

It will be seen that the curve of reaction from 100 gm. of glucose is absolutely normal, except for the glycosuria, while from 150 gm. it is diabetic in type, both as regards the time and the height of the curve, reaching a maximum of 0.188 in the hour interval.

These tests clearly indicate that the blood of normal persons differs in reaction to sugar ingestion from the diabetic's only in degree. In the diabetic, if the dose is small enough or the disease mild enough, a normal curve can be obtained. In the normal, if the dose is large enough for the individual, a diabetic curve can be obtained. This curve may belong either to the mild or the severe type as found in diabetes mellitus.

DISCUSSION AND SUMMARY

No discussion of the results found in this work would be complete without reference to the animal experiments reported by Lusk [14] and by Fisher and Wishart.[15] These authors studied the metabolism of the dog after the absorption of dextrose and the effect of such absorption on the composition of the blood. They found that after the ingestion of 50 gm. dextrose in 150 c.c. water there is a rapid absorption of dextrose during the first hour, the sugar in the

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14. Lusk, G.: J. Biol. Chem. **13**:27, 1912.
15. Fisher, G., and Wishart, M. B.: J. Biol. Chem. **13**:49, 1912.

blood rises above its normal content, and the hemoglobin content is not profoundly changed. At the end of the second hour, between two-thirds and three-fourths of the sugar has been absorbed, the blood sugar percentage has become normal, and the blood usually is more dilute. The dilution takes place as a result of the increased osmotic power of the blood, due to the increase in sugar content found at the end of the first hour. This condition lasts through the third hour, while during the fourth hour the absorption of dextrose is completed. The urinary secretion suddenly increases, the hydrémic plethora tends to diminish, and this hour is the last hour of increased metabolism which has started in the first hour. With the return of the blood to its normal volume, the percentage content of dextrose is not altered through the concentration of the blood. One experiment is reported in which a dog received only 20 gm. of dextrose and the protocol shows a practically complete absorption at the end of the hour with little change in blood volume. With larger amounts than 50 gm. the absorption in the dog is slower and reaction in the blood more prolonged.

These experiments prove conclusively that after giving glucose, the possibility of blood sugar changes being due to changes in blood volume must be taken into account. The dog experiment in which only 20 gm. glucose was given more nearly simulates the test as outlined in this paper; since the giving of 50 gm. dextrose to a 9 kg. dog would be equivalent to giving approximately from 250 to 300 gm. dextrose to a man weighing 50 kg. It is again to be noted that in the dog experiment in which only 20 gm. was given, absorption was complete in one hour and the change in the blood volume was very slight. Bailey [5] in his work attempted to study blood volume, and his charts show only slight changes after the ingestion of 75 gm. dextrose by the normal man.

Although consideration of this work makes it necessary to bear in mind that blood sugar percentage reaction to glucose ingestion may not be an index of disturbed metabolism, it does not interfere, we believe, with certain clinical deductions which can be drawn from the test. Diseases associated with disturbed carbohydrate metabolism do not necessarily present either glycosuria or hyperglycemia as ordinarily understood by the single test. The diabetic may at certain times of the day give a normal blood sugar and show no glycosuria (Mosenthal [16]). In exophthalmic goiter, hyperglycemia is the exception rather than the rule. On the other hand, not all persons showing glycosuria are diabetic. Protocols of my experiments show that the blood sugar

16. Mosenthal, H. O.; Clausen, S. H., and Hiller, A.: Arch. Int. Med. **21:** 93 (Jan.) 1918.

reaction of the diabetic to ingested glucose represents a quantitative rather than a qualitative variation from normal. This reaction is not specific for diabetes, as an identical reaction may be found in a variety of other conditions.

The normal curves reach their height of 0.145 in thirty minutes. The severe diabetic ascended to any height at any time, but rarely before an hour, and dropped to normal slowly. Apparently the first change toward the abnormal is the delay in reaching the height of the curve, as can be seen in the reaction of the mild diabetic, which reached its height in the hour and dropped quickly. Variations from the strictly normal curve suggest a disturbance of sugar mobilization at the time of the test, and this disturbance bears a quantitative relationship to the type of curve presented. At the present time, the reaction cannot be interpreted to mean diabetes or a disturbance of carbohydrate metabolism identical with diabetes, since a similar reaction is found in so many unrelated conditions. Nevertheless, alimentary hyperglycemia has a value in a differential diagnosis in obscure cases— a value entirely nonspecific and relative to other clinical and laboratory data obtained in the individual case.

RENAL GLYCOSURIA *

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III

The diagnosis of renal glycosuria is based on the syndrome of (1) glycosuria without hyperglycemia, (2) glucose excretion almost entirely independent of carbohydrate intake, and (3) absence of diabetic symptoms. To these data should be added, I think, a fourth, namely, that such patients do not subsequently develop diabetes mellitus or show a disturbance of carbohydrate metabolism similar to that found in diabetes mellitus. Not many reported cases have been observed long enough to answer either of the latter two questions. Garrod's [1] case was observed six years, Goto's [2] five years. Allen, Wishart and Smith [3] have recently recorded three cases of renal glycosuria, and have discussed the unsatisfactory nature of this interesting anomaly. It is the purpose of this paper to place on record four cases, patients who have been under observation for from two to eight years since the onset of the disease and on two of whom late metabolic studies were possible.

Glycosuria without hyperglycemia is certainly no longer sufficient evidence on which to base a diagnosis of renal glycosuria, as this combination may be found in patients with mild but true diabetes mellitus. Early cases of diabetes mellitus, those, for instance, discovered in life insurance examination, not infrequently show an excretion of glucose not dependent entirely on carbohydrate intake. In such cases the discovery of glycosuria may precede the onset of typical diabetic symptoms. Study of the cases reported in the literature as renal glycosuria forces the belief that probably not all cases belong to the same class (Strouse and Beifeld [4]). The ultimate outcome or late development in only a few cases is on record. The blood sugar response to ingested glucose has been reported rarely, and the reported results are not entirely uniform. Lewis and Mosenthal [5] record one case with a normal blood sugar curve. Allen, Wishart and Smith [3] say that the low blood sugar values "after large starch or sugar ingestion

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1. Garrod, A. E.: Brit. M. J. **2**:850, 1913.
2. Goto, K.: Arch. Int. Med. **22**:96 (July) 1918.
3. Allen, F. M.; Wishart, M. B., and Smith, L. M.: Arch. Int. Med. **24**:523 (Oct.) 1919.
4. Strouse, S., and Beifeld, A. H.: J. A. M. A. **62**:1301 (April 25) 1914.
5. Lewis, D. S., and Mosenthal, H. O.: Johns Hopkins Hosp. Bull. **27**:133, **1916.**

stand in contrast not only to the conditions in diabetes, but also to the hyperglycemia of normal persons after feeding." Yet Paullen's patient [6] showed a blood sugar response to ingested glucose distinctly of the abnormal "metabolic" type. Janney [7] has called attention to the abnormal hyperglycemic curve in Paullen's case. The cases which form the basis of this report shed some light both on the blood sugar reaction and on the clinical course.

REPORT OF CASES

CASE 1.—This man was first seen in December, 1912. He was then 23 years old. He was refused life insurance in November on account of sugar in his urine, which was his reason for consulting us. He had no complaints, no increased appetite, polydypsia or polyuria, and had not lost weight.

Past History.—Five years before he had possibly had typhoid fever. He denied syphilis. He was always a "high liver" and had eaten of rich foods plentifully. He had used alcohol moderately, smoked cigarets freely, and was of a nervous, excitable temperament. About one year before he was in a sleighing accident and was thrown to the street, landing on his head. Unconsciousness lasted only a few minutes, when he arose and drove an automobile home. He had intense headaches for three or five days at that time. He was examined by a competent physician who found no evidence of skull fracture. The urine had been examined shortly before and shortly after the accident but no sugar had been found.

Family History.—There is no diabetes in the family, but all members belong to the high strung, neurotic type.

Examination.—Physical examination (1912) was very thoroughly made and was completely negative. The Wassermann test was negative.

COMMENT

Without going into details on the course of the study made at that time, which has been previously reported [4] it can be said in brief: (1) that he had a glycosuria practically independent of carbohydrate intake; (2) that it was possible to render him sugar free only one time, for a period of a few days; (3) acidosis and clinical signs of acid intoxication developed on carbohydrate withdrawal more quickly than in the normal; (4) restriction of protein intake did not reduce the glycosuria, and (5) the blood sugar both during starvation and after a full meal was normal. (The original blood sugar determinations were from Von Noorden's clinic.) Early in 1913 the patient decided to try to force the issue. If diabetes were present he wanted to know it at once. Consequently he ate anything and everything that he wished and has continued to do so up to the present. He has been under constant observation. At no time has urinary sugar disappeared, and at no time was a hyperglycemia demonstrated in a single examination. In May, 1919, practically seven years after

6. Paullen, J. E.: J. A. M. A. **75**:214 (July 14) 1920.
7. Janney, N. W.: J. A. M. A. **75**:217 (July 14) 1920.

the onset, the patient put himself under closer observation. His history during the past years was that of a perfectly normal man. He had grown stout, had been under no dietary restrictions whatever, and had shown no symptoms of diabetes mellitus. *His urine contained more sugar.* He had been for the past few months indulging in sweets and had been drinking more freely of alcoholic beverages, as he had been acting as official taster of syrups and alcoholic drinks in a big hotel. On May 15, 1919, he was given 100 gm. glucose in 200 c.c. of lemonade, with the results shown in Table 1.

TABLE 1.—Sugar Curve of Mr. B. After Ingestion of Glucose

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar, Gm. per Hour	Urine Quantity, C.c.
8:45 a.m.	0.142	3.0	....	120
9:00 a.m. (100 gm. glucose)				
10:00 a.m.	0.27	0	0	0
10:15 a.m.	....	2.8	1.4	75
10:30 a.m.	0.31	0	0	0
11:00 a.m.	0.33	0	0	0
11:30 a.m.	0.36	3.0	2.16	87

TABLE 2.—Sugar Curve of Mr. B., After Ingestion of Glucose, June 6, 1919

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar, Gm. per Hour	Urine Quantity, C.c.
8:30 a.m.	0.09	0.75	....	28
8:35 a.m. (100 gm. glucose)				
9:05 a.m.	0.10	1.0	0.48	24
9:45 a.m.	....	2.7	2.88	80
10:05 a.m.	0.14	0	0	0
10:35 a.m.	0.10	3.8	4.56	90

This result was extremely surprising. The hyperglycemic curve was definitely diabetic in type (see last article) and the sugar excreted was high. Up to a short time before this test, the amount of sugar excreted had always been so small that quantitative determination by ordinary clinical procedures had been impossible (the new Benedict[8] method was not employed). This sugar gave typical tests for glucose. May 19, 1919, a blood sugar curve taken at 12 noon was 0.05. It was considered possible that the high carbohydrate feeding in the past few months had broken down his tolerance and that the patient had become diabetic. He was requested to refrain from this excessive carbohydrate and alcohol intake but to make no other restrictions in his diet. He returned for a subsequent alimentary test on June 6, 1919, when he was again given 100 gm. glucose in 300 c.c. lemonade.

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8. Benedict, S. R.: J. Biol. Chem. **34**:195, 1918.

This test, as far as the blood sugar curve is concerned, is definitely normal except for the delay in reaching its maximum. May 19, 1919, a Mosenthal test meal was given. The meal consisted of 1,760 c.c. fluid—13 gm. nitrogen, 11 gm. salt, 81.25 gm. protein and 162 gm. carbohydrate. The results are shown in Table 3.

TABLE 3.—REACTION OF MR. B. AFTER MOSENTHAL TEST MEAL

Time	Quantity Urine, C.c.	Specific Gravity	Sugar, Gm.	Sodium Chlorid, Gm.	Total Nitrogen, Gm.	Urea Nitrogen, Gm.
8–10 a.m.	285	1.018	1.48			
10–12 a.m.	75	1,025	0.50			
12– 2 p.m.	215	1.022	2.41			
2– 4 p.m.	190	1.025	2.41	13.71	8.44	2.51
4– 6 p.m.	145	1.027	0.61			
6– 8 p.m.	145	1.026	0.84			
Total, day...........	1,055	.....	8.25	13.71	8.44	2.51
8 p.m. to 8 a.m.	350	1.029	2.97	3.57	4.45	1.97
Total.............	1,405	.....	11.22	17.28	12.89	4.48

This reaction to the Mosenthal test meal is not altogether normal. An excess of sodium chlorid and of nitrogen is excreted, and the urea nitrogen is low. There is no fixation and no retention of total nitrogen. May 20, 1919, the phenolsulphonephthalein test showed in the first hour 23 per cent., and in the second hour 9 per cent., a depression of excretion. As in Allen's three recent cases, the subnormal phthalein excretion is the only indication of any renal retention. Although in our case the test for renal function was done seven years after onset, there seems to be no depression of renal function.

This patient was not seen again until the summer of 1920. July 20, 1920, he was given 100 gm. glucose in 300 c.c. lemonade, with the results shown in Table 4.

TABLE 4.—SUGAR CURVE OF MR. B., JULY 20, 1920, AFTER INGESTING GLUCOSE

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar, Gm. per Hour	Urine Quantity, C.c.
9:00 a.m.	0.10	0.41	....	90
9:10 a.m. (100 gm. glucose)				
9:40 a.m.	0.20	0.81	0.55	50
10:10 a.m.	0.156	1.39	1.388	50
11:10 a.m.	0.142	1.31	1.64	125
12:10 p.m.	0.117	1.91	1.81	95

This reaction, when compared with the reactions discussed in the previous paper, will be seen to be abnormal in type. The maximum rise to 0.20 is higher than seen in our normal controls, although unlike the typical metabolic curves the height is reached in the half hour. However, the maintenance of the level of 0.156 in the hour and the slow drop are strongly suggestive of a metabolic type.

CASE 2.—A young man, 13 years of age, was first seen in May, 1916. Sugar had been found in his urine accidentally at that time in the course of a routine urine examination in preparation for tonsillectomy. He had had several attacks of acute tonsillitis and the usual infectious diseases of childhood. He had no symptoms of diabetes. His family history was completely negative.

Physical Examination.—He was an unusually robust young chap, and except for the presence of sugar in the urine the physical examination was completely negative. At the time he was first seen he had been on a carbohydrate free diet for three weeks. Despite the presence of a small amount of urinary sugar his blood sugar was only 0.05.

He was not treated for diabetes but was told to lead a normal life, only omitting sugar and food containing sugar. From this time, May, 1916, to June, 1918, he was watched constantly. Growth and development had been normal; the trace of sugar, too small to measure quantitatively by usual clinical procedures, was constantly present. Several blood sugars were done during this period; these were normal or subnormal.

COMMENT

No symptoms of diabetes have arisen. In June, 1918, he became sugar free and was accepted as a first class life insurance risk. He also was accepted in the Reserve Officers' Training Camp. Since that time he has eaten freely of everything, including candy, sweet drinks and pastries. May 23, 1919, a sugar tolerance test was made; 100 gm. glucose in 300 c.c. lemonade was given (Table 5).

TABLE 5.—SUGAR CURVE OF C. F. AFTER INGESTING GLUCOSE

Time	Blood Sugar, Gm. per Cent.	Urine Sugar	Quantity Urine, C.c.
8:30 a.m.	0.08	0	..
8:35 a.m. (100 gm. glucose)			
9:05 a.m.	0.14	0	82
9:35 a.m.	0.05	0	53
10:05 a.m.	0.05	0	52
11:05 a.m.	0.15	Trace	40

This reaction is perfectly normal, except for the peculiar, unexplained rise of the blood sugar and the glycosuria at the two and one-half hour period. The absence of urinary sugar following the ingestion of 100 gm. of glucose three years after the onset of the disease is a striking feature. Between the date of this test and July, 1920, this young man continued to show perfect development, and during this period had his tonsils removed. He continued to be free of symptoms of diabetes although glycosuria was present more or less constantly. July 18, 1920, he was given 125 gm. glucose in 300 c.c. lemonade (Table 6).

It will be seen from Table 6 that the starvation level of 0.13 is rather higher than it should be even for a normal, and that the height of the blood sugar curve is reached in one-half hour, attaining a height of 0.19 with a slow descent to normal. The quantity of sugar in

the urine is small. This reaction, especially for 125 gm. glucose, cannot be considered pathologic; but it is like the reaction in Case 1, suggestive of a metabolic disturbance. As discussed in the previous paper, there is no specific value in the study of alimentary hyperglycemia nor is there a definitely specific variation from normal. Neither one of the tolerance tests made in 1920 on these two cases, however, can be classified as completely within normal bounds.

TABLE 6.—Sugar Curve of C. F., July 18. 1920, After Ingesting Glucose

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar. Gm. per Hour	Urine Quantity, C.c.
9:10 a.m.	0.13	0.31	....	55
9:20 a.m. (125 gm. glucose)				
9:50 a.m.	0.19	0.31	0.12	30
10:20 a.m.	0.17	0.38	0.19	25
11:20 a.m.	0.14	0.41	0.12	30
12:20 p.m.	0.13	0.45	0.13	30

CASES 3 AND 4.—It is impossible to report extensive investigations on these two patients, but they are added to this report as a matter of record, and because in one the onset was characterized by diabetic symptoms. The patients were twins, aged 11 years, first seen in January, 1918. A few weeks previously the little girl complained of irritation of the genitalia and increased thirst. Urinalysis made by her physician at that time showed sugar. The mother, having recognized that in the past both children had had the same diseases at the same time, had the boy's urine examined and was told sugar was present there, too. Both had normal deliveries with uneventful childhood.

Past History. — Both had chickenpox at the age of 5, measles at 6, and whooping cough at 8. The boy had had several attacks of acute tonsillitis and had had his tonsils removed in 1911. The girl had never had trouble with her throat. Both were heavy eaters, the boy specializing in potatoes and bread while the girl went to extremes on candy, jelly and pastries. There is no history of diabetes in the family history.

Physical Examination. — Examination at the time of the first observation showed two very healthy looking youngsters, both inclined to adiposity. Otherwise the physical examination was negative. The blood and stools were negative. The urine of both children showed a reducing substance in small amounts. which the chemical laboratory reported as glucose.

Owing to the history of increased thirst and genital irritation, these patients were considered diabetics, despite the fact that the only blood sugar made was 0.069 on each one. There seemed to be a relationship between carbohydrate intake and glucose excretion, and it had been exceedingly difficult to render these youngsters sugar free without their developing an acidosis. They were passing on an average of from 1.5 to 3 gm. sugar daily, and after the first week this amount remained fairly constant despite efforts to eliminate the sugar entirely. On semistarvation the sugar excretion rose 100 per cent., to 8 gm., and the quick onset of signs of acidosis made it inadvisable to continue treatment. Both these patients were considered at the time to

be mild diabetics of the familial type, although the low blood sugar and the difficulty of rendering them sugar free should have made us regard them as renal glycosurias even at that time. From January to April, 1918, sugar was constantly present in small amounts, but by that time the youngsters had started a revolution and eaten about what they pleased except sugar. In May, 1918, the blood sugar was 0.08 gm. per cent. No symptoms suggestive of diabetes had arisen. The children had both gained in weight and showed normal physical and mental development. At that time they began to eat everything, including sugar, candy, sweet drinks and pastries. They were not seen often, but in February, 1919, the urine of the boy became sugar free, and early in May, 1919, the girl's urine became sugar free. Both children then left the city and subsequent observation has been impossible. In July, 1920, the mother informed us that both children were perfectly normal in every way but the specimens of urine of both still contained sugar.

SUMMARY

Four cases of renal glycosuria are presented. Two patients have been under observation two years, one patient almost five years, and one patient for eight years. All four still show glycosuria. None shows symptoms of diabetes mellitus. In one, tests for renal function seven years after onset showed no depression of renal function except in regard to phthalein excretion. The two who have been observed the longest show at the end of four and eight years, respectively, a utilization of glucose that cannot be considered strictly normal, one at the end of seven years' observation showing a distinctly pathologic alimentary hyperglycemia. This may indicate the beginning of metabolic disturbance. This study emphasizes the importance of long and continued observation of all patients with this most interesting anomaly.

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